THE CANADIAN ANAESTHETISTS' SOCIETY JOURNAL

Vol. 3, No. 1 JAN., 1956

JOURNAL DE LA SOCIÉTÉ CANADIENNE DES ANESTHÉSISTES

THE CANADIAN ANAESTHETISTS' SOCIETY

EXECUTIVE OFFICERS AND COUNCIL

President

Dr. Alan B. Noble, Kingston

Past President

Dr. J. P. O'Donnell, Vancouver

Vice-Presidents

Dr. M. W. Bowering, Regina
Dr. E. W. Lunney, Saint John

Secretary-Treasurer

Dr. R. A. Gordon, Toronto

Council

Dr. J. J. Carroll, Vancouver
Dr. F. E. Lundy, Calgary
Dr. M. V. Morton, Saskatoon
Dr. D. Tass, Winnipeg
Dr. R. A. Chaplin, Toronto
Dr. R. I. Probert, Hamilton
Dr. J. E. Gorman, Windsor
Dr. J. M. Wishart, Peterborough
Dr. M. Dubeau, Montreal
Dr. H. R. Griffith, Montreal
Dr. L. Lamoureux, Montreal
Dr. R. A. P. Fleming, Halifax
Dr. A. M. R. Brown, Saint John
Dr. L. E. Prowse, Charlottetown
Dr. C. D. Kean, St. John's

THE CANADIAN ANAESTHETISTS' SOCIETY JOURNAL

Combining

PROCEEDINGS OF THE CANADIAN ANAESTHETISTS' SOCIETY
CANADIAN ANAESTHETISTS' SOCIETY NEWS LETTER

Address communications to: The Secretary, Canadian Anaesthetists' Society, 516 Medical Arts Building, 170 St. George Street Toronto 5, Canada

Printed and Published for
THE CANADIAN ANAESTHETISTS' SOCIETY, Incorporated
516 Medical Arts Building, Toronto 5, Canada

by

University of Toronto Press
University of Toronto
Toronto 5, Ontario, Canada

Annual subscription $8.00

address subscriptions to Canadian Anaesthetists' Society

Authorized as second-class matter
by the Post Office Department, Ottawa,
Canada

EDITORIAL

World Federation of Societies of Anaesthesiologists

The World Federation of Societies of Anaesthesiologists officially came into being on the 9th of September, 1955, in the closing moments of the World Congress of Anaesthesiologists at Schevenigen, in Holland. At that time the delegates of twenty-seven national societies of Anaesthesiologists met in the first Assembly of the World Federation of Societies of Anaesthesiologists; the Assembly formally adopted the Constitution and By-Laws of the Federation, elected officers and an Executive Committee, and applied for incorporation under the laws of The Netherlands.

The final embodiment of the Federation was the first fruit of an idea born at the time of the International Congress of Anaesthesiologists in Paris in 1951, and the culmination of the labours of four years by the Interim Committee set up at the Paris meeting under the chairmanship of Dr. Harold Griffith of Montreal, and with Dr. A. Goldblatt of Brussels as its able Secretary. During the week preceding the inaugural Assembly meeting the delegates of the member societies met on several occasions to discuss the Constitution and By-Laws, and the fact that only minor adjustments were made in the original drafts reflects great credit on the work of the Interim Committee.

The object of the World Federation is to make available the highest standard of anaesthesia for all the peoples of the world. In order to fulfil this object, the Constitution sets out these functions for the Federation:

1. To assist and encourage the formation of national societies of anaesthesiologists.
2. To promote the dissemination of scientific information.
3. To recommend desirable standards of training for anaesthesiologists.
4. To provide information regarding opportunities for postgraduate training and research.
5. To encourage research into all aspects of anaesthesiologists.
6. To encourage the establishment of safety measures including the standardization of equipment.
7. To advise, upon request, national and international organizations.

It would seem to us that, aside from activity directed at providing training of a high standard for all who desire it, one of the most important ways of exercising these functions will be in the organization of World Congresses of the type recently held in Holland. The personal exchange of ideas and knowledge at such meetings between anaesthesiologists from all parts of the world must have an impact on the future of anaesthesiology which is only likely to be equalled by that of the mutual respect and friendship between men and women of all nations which are engendered by the personal contact and free discussion made possible by such a Congress.

World Congress of Anaesthesiologists, 1955

No matter what great meetings of anaesthetists the future may bring, the World Congress of Anaesthesiologists held at Schevenigen in Holland in September, 1955, will remain a high point in the professional life of every participant. The credit for the outstanding success of this meeting must go to the members of the Netherlands Society of Anaesthesiologists, and especially to Dr. Ritsema van Eck, the Chairman of the organizing committee; to Dr. M. Mauve, President of the Netherlands Society of Anaesthesiologists and Secretary-Treasurer of the Congress; and to Mr. Fentener van Vlissingen, the Manager of the Congress. All who have had the responsibility of organizing any sort of medical meeting will have recognized the superb organization of the Dutch Congress, and will have realized, too, that this could not have been possible without the working co-operation of many members of the Netherlands Society whose part in the great success remains unknown to their guests. A very special accolade is deserved by the wives of our Dutch colleagues, who gave so much time and energy to organizing and guiding the tours and parties designed to entertain our wives and guests, which also provided education in geography and history when we tired a little of being educated in anaesthesiology.

EDITORIAL

La Fédération Mondiale des Anesthésistes

La Fédération Mondiale des Sociétés d'Anesthésistes fut créée officiellement le 9 septembre 1955 à la fin du Congrès Mondial des Anesthésistes à Schevenigen, en Hollande, quand les délégués de 27 sociétés nationales réunis pour la première assemblie de la Fédération Mondiale des Sociétés d'Anesthésistes adoptèrent formellement la constitution et les réglements de la Fédération, élurent des officiers et un comité exécutif et demandèrent leur incorporation selon la loi hollandaise.

L'organisation définitive de cette fédération fut le premier résultat d'une idée qui vit le jour lors du Congrès International des Anesthésistes à Paris en 1951 et le fruit de quatre années de travail du comité intérimaire nommé à Paris sous la présidence du Dr Harold Griffith de Montréal et avec le Dr A. Goldblatt comme son actif sécrétaire. Durant la semaine qui précèda l'assemblée inaugurale les délégués des sociétés membres se réunirent à plusieurs occasions pour discuter de la constitution et des réglements et le fait que seulement des changements mineurs furent apportés aux projets originaux démontre la valeur du travail du comité intérimaire.

Le but de la Fédération Mondiale est d'apporter le plus haut standard de science anesthésique à tous les peuples du monde. Dans cette intention, la constitution détermine les fonctions suivantes à la Fédération:

1. Assister et encourager la formation de sociétés nationales d'anesthésie.
2. Promouvoir la diffusion de l'information scientifique.
3. Recommander des standards désirables dans l'entraînement des anesthésistes.
4. Fournir des renseignements au sujet des postes disponibles pour entraînement ou recherche.
5. Encourager la recherche dans tous les sujets reliés à l'anesthésie.
6. Promouvoir l'établissement de mesures de sécurité incluant la standarisation de l'équipement.
7. Conseiller sur demande, les organisations nationales et internationales.

Il nous semble, qu'en plus de l'effort pour fournir un entraînement supérieur à tout ceux qui le désirent, l'une des plus importantes manières d'exercer ces fonctions sera dans l'organisation de Congrès mondiaux semblables à celui récemment tenu en Hollande. L'opportunité qui fournit de semblables réunions d'échanger des idées et des connaissances entre anesthésistes de toutes les parties du monde devrait faire sa marque sur le futur de l'anesthésie et également promouvoir le respect mutuel et l'amitié entre hommes et femmes de toutes les nations par le contact personnel et la discussion libre rendus possibles par un tel Congrès.

Le Congrès Mondial des Anesthésistes, 1955

Quelque soit l'importance des futurs congrès d'anesthésie, le Congrès Mondial tenu à Schevenigen en Hollande en septembre 1955 restera une étape re-

marquable dans la vie professionnelle des participants. Le mérite du succès exceptionnel de ce congrès doit être donné aux membres de la Société des Anesthésistes hollandais et spécialement au Dr Ritsema van Eck, le président du comité d'organisation; au Dr M. Mauve, président de la Société hollandaise d'anesthésie et sécrétaire-trésorier du congrès; à Mr. Fentener van Vlissingen, l'organisateur du congrès. Tout ceux qui ont déjà eu la responsibilité d'organiser des réunions médicales, auront admiré l'organisation superbe du Congrès hollandais et auront réalisé aussi que ceci n'a pu être possible qu'avec la coopération active de nombreux membres de la société hollandaise dont la contribution à ce grand succès demeure inconnue à leurs invités. Les épouses de nos collègues hollandais méritent les plus vifs remerciements pour avoir donné tant de temps et d'énergie à organiser visites et réceptions pour nos épouses. Ces visites et réceptions nous ont fourni aussi la possibilité d'augmenter nos connaissances en histoire et géographie quand nous étions un peu fatigués de nous instruire en anesthésie.

SOME REFLECTIONS ON THE MUSCLE RELAXANTS, WITH SPECIAL REFERENCE TO DECAMETHONIUM*

GEOFFREY ORGANE, M.D., F.F.A.R.C.S.**

MY REFLECTIONS on the muscle relaxants are provoked by the increase in their number and variety, in our detailed knowledge of their pharmacology, and in our experience of their use in clinical anaesthesia, since my first visit to Canada in 1949. True, it was already seven years since we had been scandalized by the first report from Griffith and Johnson (1) of the use of Intocostrin to produce muscle relaxation for surgical operations; but it was only three and a half years since Prescott (2) had become the first human being to be submitted to a paralysing dose of pure d-tubocurarine chloride, and little more than three years since Gray and Halton (3) had passed the milestone of their first thousand cases with Tubarine. The first clinical reports of gallamine (4) and decamethonium (5) had just been published; mephanesin, dimethyl tubocurarine, benzoquinone, laudexium, and the succinylcholines were still to come.

I can speak only from hearsay of recent pharmacological work, but a brief review is necessary as some of it has a bearing on our use of these agents in clinical anaesthesia. There was a time when the situation seemed fairly clear—there were relaxants which acted by competition with acetylcholine and there were others which simulated its action, producing depolarization of the myoneural junction. It is now evident that this classification is no longer sufficient and that many relaxants combine, to some extent, both these properties.

D-tubocurarine still ranks as a pure competition blocker of the myoneural junction (6) ("anti-depolarizing" (7) or "non-depolarizing" (8) are, perhaps, more accurate descriptions), though it is of interest that its block of the action of acetylcholine at the autonomic ganglia is by depolarization, with initial stimulation. As might be expected, its use in clinical practice has changed little, though some anaesthetists now use doses that are generous to the point of extravagance! D-tubocurarine releases histamine, and the fall in blood pressure that it induces in animals is said to be due to the histamine release, not to the ganglion block. Blood pressure fall in human beings is so rare as to occasion some doubt as to the relationship, and most of us are inclined to think that the release has a stabilizing effect on the blood pressure curve, an impression which flatters our handling of the anaesthetic. The release of histamine, however, may play a part in the comparatively rare development of bronchospasm and of massive lung collapse. Some protection from this has been claimed for antihistaminics given beforehand but, as in the treatment of all rare complications, it is difficult to be certain of the value of any preventive measure.

It should be noted that the elimination of d-tubocurarine from the body is slow, taking more than twenty-four hours. The rapid recovery from the effect of

*Presented at the Annual Meeting of the Canadian Anaesthetists' Society, Toronto, June 21, 1955.

**Westminster Hospital, London, England.

a single dose is said to be due, as in the case of thiopentone, to its redistribution in the tissues. After doses repeated to a high total, with tissue saturation, recovery is disproportionally prolonged. Anti-cholinesterases will produce temporary improvement but some residual weakness must be expected for many hours. I can see no advantage in using a larger dose than the smallest that will allow the satisfactory performance of an operation and, to my mind, too few anaesthetists make use of the remarkable potentiating effects of small amounts of ether in securing additional relaxation for the concluding stages of an operation. Such effects pass off rapidly, and completely, as the ether is eliminated.

Gallamine needs no detailed mention. It is as active as d-tubocurarine in producing parasympathetic ganglion block (9) and histamine release (4), when given in doses of equivalent paralysing effect. The predominant vagolytic action has been claimed as an advantage in preventing coughing during pneumolysis (10) but, because of the resultant tachycardia, is a disadvantage when induced hypotension is to be employed. It may be of value when the anaesthetist has forgotten to apply a topical anaesthetic before tracheal intubation.

Benzoquinone compares unfavourably with other relaxants but is of academic interest because of its intermediate position between those which produce paralysis in all animals, without initial stimulation, and those which act primarily by persistent depolarization, producing convulsive rigidity in some. Its block, like that of d-tubocurarine, will reduce the effectiveness of decamethonium and is increased by ether, yet it has anti-cholinesterase activity and is accentuated by neostigmine and edrophonium.

The first warning that the neuromuscular block produced by decamethonium was more complicated than had been thought came with reports of a curare-like block in some animals (11) and of the prolonged paralysis eventually produced in myasthenics (12), who were resistant to doses much above the normal. There were also the reduced effectiveness of successive doses and occasional unexplained cases of prolonged apnoea in apparently normal patients. A mixed depolarization and anti-depolarization block was postulated and is now generally accepted. The theories as to how this comes about are largely speculative and seem to me unnecessarily complicated. However, it appears that, with an active but transient depolarization block decamethonium produces a much less complete but more prolonged anti-depolarization block. With successive doses the anti-depolarization block becomes more complete. This, as in the case of d-tubocurarine, reduces the effectiveness of the depolarization block of subsequent doses (the so-called tachyphylaxis). Eventually the anti-depolarization block itself produces an effective paralysis with prolonged apnoea.

Many possible mechanisms have been put forward, with experimental support, to account for the occasional prolonged paralysis following suxamethonium—lowered plasma cholinesterase (13), carbon dioxide retention (14), accumulation of succinylmonocholine (15), and dual block. None of these is wholly satisfying as an explanation but any or all could play a part. Until the position is further clarified it must be assumed that, in those cases where anti-cholinesterases have produced an increase in muscle tone, an effective anti-depolarization block has been present. Apart from the obvious error of carbon dioxide accumulation, these

are effects of a relative over-dose and can probably be avoided by following the fundamental principle of varying the dose to the needs of the individual patient (16). It seems unwise to complicate the issue by using suxamethonium when its effectiveness has already been reduced by a previous injection of d-tubocurarine.

One of my objects is to give a brief account of the use of decamethonium in anaesthetic practice and to suggest that it has certain advantages because of which it might be more widely employed. Nearly as much decamethonium is used at Westminster Hospital as in the rest of Great Britain put together. The reason for its general unpopularity is the lack of an effective antidote. This reason has never impressed us. In general, we take the view that the correct dose of any agent is the smallest that will produce the required effect: and that any technique which includes the routine use of an antidote must be regarded with suspicion. Though we do not hesitate to use neostigmine or edrophonium when we consider it necessary, this necessity is unusual and we regard it as evidence of our misjudgment of the dose of relaxant.

Accordingly, we have persisted with decamethonium and we now have an experience of several thousand cases, extending over the last six years. It has been used for nearly all types of operation and a general pattern of the range of its usefulness has begun to emerge.

The initial dose, in adults, has varied from as little as 2 mgm. to as much as 12 mgm. A dose of 3 mgm. will often not produce adequate muscle relaxation for an upper abdominal operation, though it would be suitable for interval appendicectomy. I would use 3 mgm., too, for low segment Caesarian section where full muscle paralysis is not necessary and where, in spite of experimental evidence that decamethonium does not cross the placenta, I prefer not to run the risk of any muscle weakness in the child. Otherwise, I give 4 mgm. when the operation is expected to last not longer than 20 or 25 minutes, and 5 mgm. if it is to be half an hour or more. This dose usually produces apnoea, which is my aim for reasons I shall mention later. Respiration is controlled by hand and, at the first sign of spontaneous breathing, or if muscle relaxation becomes inadequate, a further dose of relaxant is given. When the operation appears to be nearing completion, suxamethonium is the most satisfactory; otherwise 3 to 5 mgm. of decamethonium is injected, according to the patient's reaction to the initial dose. Of suxamethonium, 10 to 20 mgm. is usually sufficient and can be repeated as required. Full relaxation with apnoea for as long as half an hour, in these circumstances, can usually be produced with a total dose of 60 mgm. or less.

One of the most attractive features of decamethonium is the very sharp end point. Provided a suitable period has elapsed since the previous injection, it may take as little as one minute from the first attempt at breathing to the establishment of what appears to be full respiratory muscular activity. Not only is there no need for any antidote, but there is no anxiety that a combination of central respiratory depression with residual muscular weakness, which is invariably present to a greater or less degree with d-tubocurarine, may lead to a gradually mounting asphyxia and eventual respiratory failure.

The rapid recovery of respiratory function after a suitable dose of decamethonium is in accord with what we know of the more rapid recovery of active

muscle groups, compared with those that are inactive (12). Some, at least, of the abdominal muscles take part in the early respiratory movements and abdominal relaxation will pass off very soon after breathing has started. For this reason I produce apnoea by the initial dose of relaxant and maintain it for as long as possible by controlled respiration. This can prolong the period of effective abdominal relaxation by 20 to 30 per cent; by this means reduction of the dose is possible and rapid recovery ensured, and I regard it as an essential feature of the technique. There is sometimes a generalized recovery of muscle tone in a patient who is still apnoeic, but this can usually be anticipated and prevented if a careful watch is kept.

In a few cases there has been no sign of respiratory activity at the expected time, and there has been generalized flaccidity of muscles. I have not seen this after a single dose of decamethonium, but it has occurred after repeated doses to a total in excess of 10 mgm., usually of the order of 20 mgm. We assume that this is due to an anti-depolarization block and, after a suitable interval for observation, we treat it with neostigmine or edrophonium. These have proved effective and we have not, so far, seen any evidence of recurarization when the effect of the anticholinesterase has worn off. These presumed mixed blocks have been seen, also, when suxamethonium has been used to extend the period of relaxation after large doses of decamethonium (17) and they have responded in the same way to anticholinesterases.

Although they have given us no anxiety, I feel that these situations are better avoided. I think that this can be done if the total dose of decamethonium is restricted to 10 mgm., and if suxamethonium is avoided after a total of 10 mgm. of decamethonium. This implies that its use should be confined to operations where the necessary period of muscle relaxation will certainly be less than one and a half hours.

If, after repeated injections, the effect of the decamethonium appears to be diminished it is probably justifiable, in the light of our present knowledge, to assume that a significant degree of anti-depolarization block has been established. In such a case it may be wiser to continue the relaxation by cautious injection of an anti-depolarization blocker, such as gallamine, rather than a depolarizing agent. It may be that my suggested maximum dose of 10 mgm. of decamethonium is an unnecessary restriction, and that it would be a sufficient safeguard if tachyphylaxis were taxen as a sign of a developed mixed block.

Anaesthesia can be induced and maintained with the agents of choice, except ether, which has proved unsatisfactory. I have found cyclopropane the most effective, and its rapid elimination assists in the recovery of function at the end of operation. Recently I have been using thiopentone followed by demerol and nitrous oxide in most cases, to see how far I can succeed in avoiding inflammable agents. In most cases this sequence serves well enough, and the patient very quickly recovers consciousness, but it seems more difficult to handle and lacks the flexibility of cyclopropane as the anaesthesia cannot easily be deepened temporarily to cover a partial recovery of muscle tone.

Decamethonium is largely excreted unchanged in the urine and we have seen no unusual reactions which we could relate to any disease of the patient. It has

the further advantage, as far as we can tell, of having no other significant pharmacological action than that of neuromuscular block, an advantage possessed by no other muscle relaxant and most nearly approached by suxamethonium. If I were to be restricted to the use of one relaxant for all purposes I would choose d-tubocurarine but, within the limits and for the purposes I have suggested, I prefer decamethonium. It is also much less expensive than anything else!

Résumé

Il y eût un temps où la pharmacologie des curarisants était assez simple. Il y avait ceux qui agissaient par compétition avec l'acetyl choline et ceux qui simulant son action, dépolarisaient la jonction myoneurale. Aujourd'hui, il est évident que cette classification ne suffit plus et que plusieurs curarisants ont, jusqu'à un certain dégré, ces deux propriétés.

La d-tubocurarine est encore décrite comme un bloqueur par compétition de la jonction myoneurale bien qu'il est intéressant de noter que son action d'arrêt de l'effet de l'acétyl choline aux ganglions autonomiques se fait par dépolarisation. La d-tubocurarine libère de l'histamine à qui l'on attribue la chute de tension artérielle notée chez les animaux de laboratoire. Cependant, chez l'homme, une chute de tension artérielle est si rare que l'on peut doûter de cette relation. Le relâchment de l'histamine joue possiblement un rôle dans les cas peu fréquents de bronchospasme et d'atélectasie massive.

La Benzoquinone quoiqu'elle se compare défavorablement aux autres curarisants est intéressante du point de vue académique en ce que son action, comme celle de la d-tubocurarine, diminue l'efficacité du décaméthonium, est accrue par l'éther et cependant elle a une activité anticholinestérase que s'accentue avec la néostigmine et l'edrophonium.

Il est généralement admis aujourd'hui que le décaméthonium produit un effet mixte de dépolarisation et d'antidépolarisation. Quand on emploie des doses successives l'effet anti-dépolarisant devient plus complet et comme pour la d-tubocurarine, diminue l'action dépolarisante. Eventuellement l'effet anti-dépolarisant produit une paralysie efficace avec apnée prolongée. Celles-ci peuvent se traiter avec de la neostigmine ou de l'edrophonium après une période d'observation suffisante. Cet effet mixte a aussi été noté quand on emploie le suxaméthonium pour prolonger la période de relâchement après l'usage de doses importantes de décaméthonium.

L'auteur préfère employer le décaméthonium plutôt que d'autres curarisants quand la durée de relâchment musculaire requis n'est pas plus d'une heure et demie. La dose maximum doit être de préférence de 10 mgm. Si après injections répétées, l'effet du décaméthonium semble être diminué il est probablement justifiable de penser qu'une action anti-dépolarisante importante s'est établie et il peut être plus sage de continuer la curarisation en injectant prudemment un bloqueur de l'anti-dépolarisation comme la gallamine.

Le décaméthonium est excrété en grande partie comme tel dans les urines, n'a pas d'effet pharmacologique autre que de bloquer la jonction neuromusculaire et est beaucoup moins dispendieux que les autres curarisants.

REFERENCES

1. Griffith, H. R. & Johnson, G. E. The Use of Curare in General Anaesthesia. Anesthesiology 3: 418 (1942).
2. Prescott, F., Organe, G. & Rowbotham, S. Tubocurarine Chloride as an Adjunct to Anaesthesia. Lancet *1*: 80 (1946).
3. Gray, T. C. & Halton, J. A Milestone in Anaesthesia? (d-Tubocurarine Chloride). Proc. Roy. Soc. Med. 39: 400 (1946).
4. Organe, G. Decamethonium Iodide (Bistrimethylammonium Decane Diiodide) in Anaesthesia. Lancet *1*: 773 (1949).
   Hewer, A. J. H., Lucas, B. G. B., Prescott, F. & Rowbotham, E. S. Decamethonium Iodide as a Muscle Relaxant in Anaesthesia. Lancet *1*: 817 (1949).
5. Mushin, W. W., Wien, R., Mason, D. F. J. & Langston, G. T. Curare-like Actions of Tri(Diethylaminoethoxy)Benzene Triethiodide. Lancet *1*: 727 (1949).
6. Hoppe, J. O. Observations on the Potency of Neuromuscular Blocking Agents with particular reference to Succinylcholine. Anesthesiology *16*: 11 (1955).
7. Foldes, F. F. The Mode of Action of Quaternary Ammonium type Neuromuscular Blocking Agents. Brit. J. Anaesth. *26*: 394 (1954).
8. Churchill-Davidson, H. C. Abnormal Response to Muscle Relaxants. Proc. Roy. Soc. Med. *48*: 621 (1955).
9. Desmarez, J. J. Comparative Effects of d-Tubocurarine and Flaxedil on the Sympathetic System. Compt. rend. Soc. de biol. *148*: 722 (1954).
10. Ballantine, R. I. W. Anaesthesia for Thoracoplasty. Anaesthesia 7: 19 (1952).
11. Zaimis, E. J. Motor End-Plate Differences as a Determining Factor in the Mode of Action of Neuromuscular Blocking Substances. Nature *170*: 617 (1952).
12. Churchill-Davidson, H. C. & Richardson, A. T. Decamethonium Iodide (C10): Some Observations on its Action using Electromyography. Proc. Roy. Soc. Med. *45*: 179 (1952).
13. Evans, F. T., Gray, P., Lehman, H. & Silk, E. Effect of Pseudocholinesterase Level on Action of Succinylcholine in Man. Brit. Med. J. *1*: 136 (1953).
    Borders, R. W., Stephen, C. R., Nowill, W. K. & Martin, R. The Interrelationship of Succinylcholine and the Blood Cholinesterases during Anesthesia. Anesthesiology *16*: 401 (1955).
14. Davis, D. A., Ellis, F. C., Reese, N. O. & Grosskreutz, D. C. The Prolonged Effects of Succinylcholine and Some Possible Explanations for These Phenomena. Anesthesiology *16*: 333 (1955).
    Scurr, C. F. Carbon Dioxide Retention Simulating Curarization. Brit. Med. J. *1*: 564 (1954).
15. Hall, L. W. & Lehmann, H. Response in Dogs to Relaxants derived from Succinic Acid with Choline. Brit. Med. J. *1*: 134 (1953).
    Foldes, F. F. & Rhodes, D. H., Jr. Role of Plasma Cholinesterase in Anesthesiology. Anesth. & Analg. 32: 305 (1953).
16. Foldes, F. F., Vandervort, R. S. & Shanor, S. P. The Fate of Succinylcholine in Man. Anesthesiology *16*: 11 (1955).
17. Scurr, C. F. Personal communication.

UNTOWARD REACTIONS TO SUCCINYLCHOLINE*

JOHN I. DAVIES, M.D., F.R.C.P.(C), F.F.A.R.C.S., D.A.(Eng.)**

THE INTRODUCTION of curare into clinical anaesthesia by Griffith (1) in 1942 was undoubtedly a major advance in anaesthesia, aptly described by Gray as a "flash of inspired genius" (2). Little and co-authors (3) have pointed out that the sheer brilliance of Griffith's contribution has dominated the trend in the specialty of anaesthesiology for over a decade. Whatever one's opinion may be regarding the toxic potentialities of curare, the basic concept of producing muscular relaxation by a drug acting directly at the neuromuscular junction, rather than by the profound depression of general anaesthesia, is firmly established, and one must agree with an opinion expressed by Griffith in 1954, that muscle relaxants are here to stay (4).

With the general acceptance of such a revolutionary principle, it was to be expected that an intensive search would be made for the ideal muscle relaxant. Numerous drugs have been introduced and given extensive clinical trial, and of these, succinylcholine seems to come closest to the ideal requirements (5, 6). Many excellent and often enthusiastic reports on the many uses of succinylcholine have been published and reference is made to only a few of these (7–19).

Most therapeutic agents and methods, when their effectiveness has been firmly established, pass through a period of over-use, misuse and over-enthusiasm, to be followed by a phase of reaction, disappointment, and often unjustified condemnation. The purpose of this paper is to attempt to evaluate the disadvantages and untoward reactions to succinylcholine, which is an agent of proved value.

Succinylcholine is known by a wide variety of trade names and chemically also as succinyldicholine, diacetylcholine, and suxamethonium. Further confusion is added when comparing dosages of the different salts. In this paper, doses, when mentioned, will be expressed in terms of the active cation and the drug will be referred to as succinylcholine, as this name is in general use in North America.

MISUSE

If misused, any potent agent will produce undesirable effects. Like any muscle relaxant, succinylcholine will produce varying degrees of respiratory depression, and it has been emphasized repeatedly that, with all such agents, respiration must be controlled or assisted at all times if the vicious effects of anoxia and carbon dioxide retention are to be avoided.

APPARENT LACK OF POTENCY

If administration of succinylcholine does not produce the anticipated effects, it is advisable to make sure that the drug has actually been given intravenously.

*Presented at the Annual Meeting of the Canadian Anaesthetists' Society, Toronto, June 20, 1955.

**Department of Anaesthesia, Winnipeg General Hospital, and the University of Manitoba.

However, loss of potency may occur during storage of solutions. When succinylcholine chloride is stored at 75°C, the drug is 92 per cent potent in three months and 81 per cent at the end of six months (20). As the products of hydrolysis are, progressively, succinylmonocholine, succinic acid, and choline (as *in vivo*) no harm would be expected from giving a deteriorated solution, unless large amounts of succinylmonocholine were given. The pharmacology of succinylmonocholine is of importance in all considerations of the reactions to succinylcholine. Briefly, succinylmonocholine has actions similar to those of succinylcholine, but in the human about 1/40th to 1/50th of its activity, and is hydrolysed much more slowly by pseudo-cholinesterase under clinical conditions (21, 22).

On five separate occasions when using a solution of succinylcholine chloride by continuous intravenous drip, I did not obtain the effect one would expect, and when a change was made to an intravenous drip of a freshly prepared solution of succinylcholine bromide powder the anticipated effect was obtained in all cases.

Resistance of patients suffering from myasthenia gravis to succinylcholine has been described (23, 24). Succinylcholine was given to five patients suffering from myasthenia gravis. In four patients receiving regular maintenance doses of prostigmine, 60 mgm. of succinylcholine produced an expected and normal response. The fifth patient, who had not received any prostigmine, was not relaxed at all with 60 mgm. of succinylcholine, and a further dose of 60 mgm., given within one minute, produced only a very slight effect of muscular relaxation.

Muscle Twitchings or Fasciculations

Though frequently seen, muscle fasciculations cause few reported complications. Postoperative muscle soreness lasting for a few days sometimes occurs. The muscle fasciculations were originally attributed by Foldes (25) to the initial stimulating effect of a depolarizing compound on skeletal muscle, but Paton (26) has suggested that the fascicular twitching is due to centripedal antidromic impulses in the motor nerve axon, which bring about a synchronous discharge of the whole motor unit. Churchill-Davidson (27) found that when the injection of succinylcholine was preceded by 40 mgm. of Flaxedil, visible muscle twitching was invariably abolished and the incidence and severity of muscle pains were diminished but not abolished. It has been reported that muscle fasciculations are stronger when the level of plasma pseudo-cholinesterase is high. The severity of muscle twitching and after pains seems to be related to the rate of injection and depth of general anaesthesia, and for this reason it has been suggested that succinylcholine is unsuitable for use as a muscle relaxant for outpatient procedures. In the cases in which I have used succinylcholine, severe muscle stiffness was noted in seven patients all of whom had been anaesthetized for minor procedures, and this gives an incidence of roughly 1.2 per cent. Unfortunate displacement of fracture ends has resulted from violent muscle spasm preceding manipulation.

Effects on the Autonomic Nervous System

These have been carefully looked for, and as succinylcholine is closely related chemically to acetylcholine, it is not surprising that both muscarine and nicotine-like effects may be produced.

Salivation is often noted and is sometimes profuse, particularly during light anaesthesia and in patients who have not received adequate dosage of atropine (or other drying agents). Hypersecretion of bronchial glands does not appear to occur.

Laryngeal and bronchial spasm, though they may occur, are not directly attributable to succinylcholine and are caused by errors in technique, such as failure to complete intubation before the relaxing effects have worn off, or by the irritating effects of an endotracheal tube (particularly if the cuff is inflated), if the patient is inadequately anaesthetized.

Effects on the Cardiovascular System

Some observers have reported few significant clinical effects of succinylcholine on the cardiovascular system. However, on closer investigation many effects have been recorded. Cardiac irregularities on endotracheal intubation with various combinations of agents have been described, so it is not surprising that similar reactions occur when succinylcholine has been used to facilitate intubation.

Somers (28), investigating the effects of succinylcholine on the cardiovascular system of cats and dogs, found an obvious nicotinic effect in most animals, but no evidence of a muscarine effect. Clinically the commonest reactions are elevated blood pressure, cardiac irregularities and bradycardia, followed by tachycardia in about 40 per cent of one series of cases (29). Bourne has described an increase in the height of the T-wave from 2 to 4 mm. (30), and Phillips (31) found various changes following endotracheal intubation, including cardiac irregularities as shown on the electrocardiographic tracing, such as auricular standstill, nodal rhythm, and ventricular extra systoles. However, the number of cases in which succinylcholine was given before and after pentothal anaesthesia were not reported, nor was the incidence of the observed untoward effects; though it was pointed out that most of the physiological changes could be avoided if succinylcholine were administered following intravenous barbiturate anaesthesia.

Johnstone (32), investigating the effects of succinylcholine on the cardiovascular system of 100 patients who had been premedicated with atropine and anaesthetized with small doses of pentothal, found slight slowing of the pulse in 28 cases, and definite bradycardia in 32 cases with pacemaker shift to the A-V node in 7 patients. This bradycardia was usually followed in about two minutes by a brisk tachycardia. These muscarine effects could be modified by atropine, but not always prevented in the dosage prescribed. In 30 per cent of his cases, flattening of the T-wave with depression of the S T segment was seen. This was not influenced by atropine, and was unrelated to heart rate. He described four instances of severe cardiovascular collapse following administration of succinylcholine to fit young men. These changes are similar to those caused by acetylcholine. However, in spite of all these effects, Johnstone concluded that succinylcholine provides better and safer conditions for endotracheal intubation than other relaxants.

Regarding blood pressure changes, one often sees a slight transient hypertension after a single dose, and prolonged mild hypertension after continuous

drip infusion of succinylcholine. The initial hypertension has been attributed to an asphyxial type of response in the absence of adequate ventilation, possibly aggravated by the muscular activity. The prolonged pressor response is attributed by Paton (33) to the nicotinic effects of succinylcholine and succinylmonocholine and these are not influenced by atropine.

Griffith (34) has emphasized that insidious carbon dioxide accumulation cannot always be excluded as a contributing factor to these late rises in blood pressure.

Little (35) found an infusion of succinylcholine a very useful agent in the anaesthetic technique for mitral commissurotomy and found no deleterious effects on the cardiovascular system in these seriously ill patients.

Release of Histamine

In large doses succinylcholine can cause histamine release, but is about 100 times less liable to do so than d-tubocurarine. As much larger doses of succinylcholine may be given, even a comparatively slight activity of this sort may be of significance (36), though this does not seem to be of practical importance.

Insufficient Anaesthesia

Cases of patients regaining consciousness while paralysed with curare have been recorded (37); this unpleasant complication has occurred in one of my cases, and I have heard first hand of two others (38).

Succinylcholine in Obstetrics

Succinylcholine has been shown by Pittinger and co-workers (39) to be capable of crossing the placental barrier if the concentration in the uterine artery is sufficiently high. Stead (40), using succinylcholine in 300 neonates, found no prolonged response in spite of the infants' low normal pseudo-cholinesterase level. Succinylcholine has been used by many anaesthetists in combination with general anaesthesia during Caesarian section, and also to produce perineal relaxation during vaginal delivery (41), but no case of respiratory depression of the babies has been attributed to the use of succinylcholine.

Respiratory System

As with all muscle relaxants, when succinylcholine produces muscular relaxation there is depression of respiratory activity, and the "relative sparing effect on respiration" reported by Foldes (42) in 1952 has not been confirmed. However, as the degree of relaxation is controllable when a continuous drip is used, it is often possible to produce relaxation adequate for surgical procedures, with minimal respiratory depression.

The most important clinical untoward effect with succinylcholine has been prolonged apnoea, and this complication has been reported at least fifty times, including some interesting cases (43–54). The incidence of prolonged apnoea is given by Bourne (55) as 15 out of 1000 patients. Of these, ten had a pseudocholinesterase level below normal or low normal.

Using succinylcholine in over 600 cases, I have encountered three patients who were unusually sensitive to the drug. In one patient suffering from ulcerative colitis, 60 mgm. of succinylcholine produced apnoea for 10 minutes, and abdominal relaxation was adequate for 1½ hours with a further 100 mgm. by intermittent intravenous drip. A patient suffering from abdominal obstruction was apnoeic for 35 minutes after 60 mgm. of succinylcholine and this period of profound relaxation was long enough for the operation to be completed.

Succinylcholine (in 60 mgm. dosage) was given to 87 patients with known clinical liver damage, and of these one patient was unduly sensitive to succinylcholine. A dose of 60 mgm. produced apnoea for 29 minutes, the return of muscle tone and respiratory activity being quite sudden. Subsequent intermittent doses of succinylcholine were given to provide muscular relaxation for the operation (cholecystectomy) and produced apnoea for the following times:

20 mgm.	10 min.
20 mgm.	13 min.
10 mgm.	9 min.
10 mgm.	16 min.
5 mgm.	20 min.
2 mgm.	10 min.
2 mgm.	21 min.

Near completion of the operation, one bottle of stored blood (four days old) was given and after this 2 mgm. of succinylcholine produced apnoea for 6 minutes. From these figures it would seem that although cumulative effects of succinylcholine are not seen in normal patients (56), increasing sensitivity may be present in patients who show an abnormal response. This patient was a farmer's wife, but denied contact with organic phosphorous insecticides. Unfortunately it was not possible to estimate her pseudo-cholinesterase level at that time.

The cause of prolonged apnoea is not always clear, as many different factors may be involved. At one time prolonged apnoea was attributed by Foldes (57) simply to over-dosage, but other factors include: (1) the associated respiratory depressant drugs used; (2) acapnoea from hyperventilation; (3) distension of the lungs interfering with the Hering-Breuer reflex; (4) a direct depressing effect of succinylcholine on the respiratory centre (58); (5) hypo-calcaemia associated with muscular spasms (59); (6) temporary interference with the electrolite balance, particularly potassium imbalance; (7) the muscle relaxing effects of succinylmonocholine produced by incomplete hydrolysis; (8) carbon dioxide retention and anoxia. The latter is probably an important factor, as in many reported cases recovery of consciousness was delayed beyond expectation.

However, it seems clear from the work of Evans and co-workers (60), that the usual cause of prolonged apnoea is a lowered plasma pseudo-cholinesterase level, and a definite correlation has been shown to exist between the pseudo-cholinesterase level and the duration of apnoea following succinylcholine.

Pseudo-cholinesterase levels have been investigated in health and disease (61) and low levels have been shown to be sometimes present in cases of liver disease, cachexia, and anaemia and in the severe malnutrition of Kwashiorkor (62). A delayed recovery may be seen in cases of intestinal obstruction, and an increased

response to succinylcholine has been shown to occur in rats following experimental intestinal trauma (63).

Low levels of cholinesterases can be expected in patients after administration of anti-cholinesterases such as prostigmine and Tensilon, and exposure to alkyl pyrophosphates (such as D.F.P.) used in agriculture as insecticides. As pseudo-cholinesterase hydrolyses other esters, the simultaneous administration of succinylcholine and a local anaesthetic agent containing an ester linkage can be expected to cause a prolonged effect of succinylcholine, and this has been confirmed (64).

Low pseudo-cholinesterase levels can occur in patients healthy in other respects (65) and Forbat (66) has described a family of Cypriots with an unexplained low pseudo-cholinesterase level, presumably a genetic inheritance. Callaway (67) has stated that the incidence of patients with low pseudo-cholinesterase level must be extremely rare in healthy subjects. However, the estimation may be desirable under some circumstances. At least four different methods of estimation have been described, each of which expresses the results by a different means. The commonest method seems to be the Warburg manometric method of McArdle (68); by it normal figures are said to be 80–130 units per cc. of plasma. To avoid confusion, Hink (69) has suggested that clinical units be adopted, 1 clinical unit being defined as the cholinesterase activity of 1 cc. of fresh normal pooled plasma. Thus, fresh plasma would contain about 1000 clinical units per litre. As 20 clinical units will quickly reverse the effects of 1 mgm. of succinylcholine, 1 litre of fresh plasma would be expected to neutralize 50 mgm. of succinylcholine and a healthy normal adult could be expected to deal with 300 mgm. of succinylcholine fairly quickly. On storing blood or plasma the value decreases, and stored blood could be expected to contain at least 300 clinical units per litre (70).

Pseudo-cholinesterase has been purified by Cutter Laboratories and named Cholase, and is a subfraction of Cohn's globulin fraction IV-6. Both blood (71) and Cholase (72) have proved effective in shortening the duration of apnoea, but at present Cholase is available only for clinical investigation. As 1 cc. of Cholase has a cholinesterase activity of 350 clinical units, 4–8 cc. is the recommended dose in the treatment of prolonged apnoea (73).

Some puzzling cases still remain, such as one in which a normal response was obtained after two or more injections of succinylcholine, and a final dose produced prolonged apnoea (74); in other cases a final dose of succinylcholine produced prolonged apnoea, when normal respiration had returned after using succinylcholine and other muscle relaxants (75–76); prolonged apnoea occurred after using succinylcholine in a case of myasthenia gravis, where one would expect the patient to be resistant to the effects of de-polarizing agents (77). In all these cases, the pseudo-cholinesterase level was normal and the prolonged apnoea responded to anti-cholinesterases. The probable explanation is that succinylcholine produces what Paton describes as "a dual mode of response to depolarising agents" (78). A similar explanation has been given by Hunter (79). Apart from Cholase and plasma, pharmacological antidotes are at present of little practical value, and it seems that spontaneous respiratory activity will eventually return if the patient is kept alive long enough by artificial respiration.

The longest recorded period is respiratory paralysis lasting into the third day (80) and even shorter periods must be, for the anaesthetist, a tiring and embarrassing time.

Although prolonged apnoea is rare, it is not unusual to encounter prolonged partial respiratory depression after even moderate doses of succinylcholine. This is evidenced by decreased tidal volume, tracheal tug, and probably slight cyanosis. The patients, if awake, will complain of dyspnoea. Accumulation of succinylmonocholine may be a contributing factor, but the usual cause is carbon dioxide retention with or without oxygen lack, caused by inadequate ventilation. This view is supported by the large amounts of succinylcholine which can be given without untoward effects (22.5 gm. has been given over five and a half days in the treatment of tetanus (81)); by the report by Scurr (82) of carbon dioxide retention simulating curarization; by the fact that large doses of Cholase do not reverse these particular effects (83) and that, experimentally, if dogs are ventilated with 20 per cent carbon dioxide, prolongation of muscular insufficiency caused by succinylcholine occurs (84).

The treatment is to eliminate the carbon dioxide by mechanically increasing the tidal volume, for if oxygen alone is given the improvement in colour may be deceptively dangerous.

Summary and Conclusions

The untoward effects of succinylcholine have been briefly reviewed.

The seriousness, significance, and manner of causation of these effects have been superficially discussed in the light of present knowledge.

It is concluded that the untoward effects directly attributable to the drug are either of little significance or of rare occurrence. Some are of more theoretical and pharmacological than practical interest, and most can be avoided or minimized by careful use of the drug and well-managed anaesthesia.

Résumé

L'introduction par Griffith du curare en anesthésie a établi un concept de production de relâchement musculaire par emploie de curarisants plutôt que par dépression profonde par anesthésie générale comme on procédait depuis nombre d'années. Il s'en suivit des recherches extensives pour trouver le curarisant idéal. De tous les médicaments qui ont subit l'épreuve clinique la succinylcholine semble approcher de plus près l'idéal.

Comme les autres curarisants, la succinylcholine produit une dépression respiratoire de dégré variable et l'on doit contrôler ou assister la respiration si l'on veut éviter les effets nocifs de l'anoxie et de la retention du dioxide de carbone.

Si une solution de succinylcholine ne produit pas l'effet anticipé cela peut être dû à l'injection en dehors de la veine, à la détérioration de la solution, ou encore, la résistance aux effets du médicament chez les patients souffrant de myasthénie grave.

Des contractions ou fébrillations musculaires suivent l'injection de succinyl-

choline et leur sévérité dépend de la vitesse d'injection et du dégré d'anesthésie générale. Elles causent peu de complications mais quand elles sont sévères elles peuvent occasionner des douleurs musculaires pour quelques jours. A l'occasion, un déplacement malencontreux de fracture peut se produire à la suite de violents spasmes musculaires de ce genre.

La succinylcholine peut produire des effets ressemblants à ceux de la muscarine et de la nicotine sur le système nerveux autonome. Parfois il y a salivation profuse qui ne semble pas s'accompagner d'hypersécrétion des glandes bronchiques.

On a aussi noté quelques uns des effets de la succinylcholine sur le système cardio-vasculaire. On a rapporté des élévations de pression artérielle, des irrégularités cardiaques, de la bradycardie et de la tachycardie. On a décrit quatre cas de collapse cardio-vasculaire chez de jeunes hommes en bonne condition, suivant l'administration de succinylcholine.

La reaction la plus nuisible que peut suivre l'emploie de la succinylcholine est une apnée prolongée. La plupart des patients qui en souffrent ont une pauvre concentration plasmatique active de pseudo-cholinestérase. Cependant, chez certains, la cause est inconnue. Comme autres facteurs on peut inclure: (1) l'usage d'autres dépressifs respiratoires; (2) l'acapnée due à l'hyperventilation; (3) la distension pulmonaire perturbant le reflexe d'Hering-Breuer; (4) un effet dépressif direct de la succinylcholine sur le centre respiratoire; (5) l'hypocalcémie qui accompagne les spasmes musculaires; (6) les modifications temporaires de l'équilibre électrolytique, particulairement le déséquilibre du potassium; (7) les effets de relâchment musculaire de la succinylcholine produits par hydrolyse incomplète; (8) la retention du dioxide de carbone et l'anoxie. L'apnée prolongée, dans certains cas, peut être due à la "double réaction" décrite par Paton.

On peut conclure en disant que les effets nuisibles qui peuvent être attribuer directement au médicament sont de peu d'importance ou se produisent rarement. La plupart peuvent être évités ou diminués en employant le médicament prudemment et en donnant une bonne anesthésie.

REFERENCES

1. Griffith, H. R. & Johnson, G. E. The Use of Curare in General Anaesthesia. Anesthesiology *3*: 418 (1942).
2. Gray, T. C. D-Tubocurarine Chloride. Proc. Roy. Soc. Med. *41*: 559 (1948).
3. Little, D. M., Hampton, L. J. & Grosskreutz, D. C. Succinylcholine (Diacetylcholine), a Controllable Muscle Relaxant. Anesth. & Analg. *32*(3): 171 (1953).
4. Griffith, H. R. Succinylcholine—A Controllable Muscle Relaxant. C.M.A.J. *71*(1): 28 (1954).
5. Gillies, D. M., Cullen, W. G. & Griffith, H. R. Succinylcholine as a Relaxant in Abdominal Surgery. Anesth. & Analg. 33(4): 251 (1954).
6. Little *et al.* Anesth. & Analg. *32*(3): 171 (1953).
7. Ottolenghi, R., Manni, C. & Mazzoni, P. A New Short-Acting Curarising Agent. Anesth. & Analg. *31*(4): 243 (1952).
8. Von Dardel, O. & Thesleff, S. Clinical Experience with Succinylcholine-Iodide: A New Muscle Relaxant. Anesth. & Analg. *31*(4): 250 (1952).
9. Adamson, D. C. & Kinsman, F. M. Succinylcholine Chloride in Anaesthesia. Anaesthesia 7(3): 166 (1952).

10. Thesleff, S., von Dardel, O. & Holmberg, G. Succinylcholine Iodide. Brit. J. Anaes. *24*(4): 238 (1952).
11. Foldes, F. F., McNall, P. G. & Borreco-Hinojosa, J. M. Succinylcholine: A New Approach to Muscular Relaxation in Anaesthesiology. Proc. Can. Anaes. Soc.: 38 (1952).
12. Swerdlow, M. Continuous Suxamethonium for Relaxation in Abdominal Surgery. Brit. J. Anaes. *25*(2): 130 (1953).
13. Gordon, R. A. & MacKay, I. M. A Report of the Use of Succinylcholine in Anaesthesia. Proc. Can. Anaes. Soc.: 44 (1953).
14. Martin, R. C., Nowill, W. K. & Stephen, C. R. An Evaluation of Succinylcholine. Anesthesiology *15*(2): 179 (1954).
15. Hampton, L. J., Little, D. M. & Fuller, E. M. The Use of Succinylcholine to Facilitate Endotracheal Intubation. Anesthesiology *14*(4): 382 (1953).
16. Carlson, C. O., Norberg, R. W., Joseph, S. I. & Denson, J. S. Clinical Evaluation of Succinylcholine in 1000 Anaesthetized patients. Anesth. & Analg. *33*(2): 135 (1954).
17. Bourne, J. G., Collier, H. O. J. & Somers, G. F. Succinylcholine: Muscle Relaxant of Short Action. Lancet 2: 1225 (1952).
18. Swerdlow, M. Continuous Intravenous Infusion of Succinylcholine (A Milestone in Relaxation?). Anesth. & Anal. *33*(3): 201 (1954).
19. Woolmer, R. & Gates, J. E. Treatment of Tetanus with Succinylcholine. Lancet 2: 808 (1952).
20. Gwinn, R. P. Personal communication.
21. Collier, H. O. J. & MacAuley, B. M. Succinylmonocholine. Letter to Editor, Brit. Med. J. *1*: 1279 (1953).
22. Foldes, F. F., McNall, P. G. & Birch, J. H. The Neuromuscular Activity of Succinylmonocholine Iodide in Anaesthetized Man. Brit. Med. J. *1*: 967 (1954).
23. Churchill-Davidson, H. C. & Richardson, A. T. Variation Response to Relaxant Drugs. Letter to Editor, Lancet 2: 1228 (1951).
24. Ginsberg, H. & Varejes, L. The Use of a Relaxant in Myasthenia Gravis. Anaesthesia *10*(2): 177 (1955).
25. Foldes, F. F. *et al.* See item 11.
26. Paton, W. D. M. Discussion on Decamethonium Iodide (C.10). Proc. Roy. Soc. Med. *45*: 186 (1952).
27. Churchill-Davidson, H. C. Suxamethonium (Succinylcholine) Chloride and Muscle Pains. Brit. Med. J. *1*: 74 (1954).
28. Somers, G. F. Studies on the Pharmacology of Succinylcholine. Brit. J. Phar. *8*: 19 (1953).
29. Green, R. Controlled Relaxation with Succinylcholine Chloride. Anaesthesia *8*(1): 52 (1953).
30. Bourne, J. G. *et al.* See item 17.
31. Phillips, H. S. Physiologic Changes noted with the Use of Succinylcholine Chloride as a Muscle Relaxant during Endotracheal Intubation. Anesth. & Anal. *33*(3): 165 (1954).
32. Johnstone, M. Relaxants and the Human Cardio-Vascular System. Anaesthesia *10*(2): 122 (1955).
33. Paton, W. D. M. Principles of Neuromuscular Block. Anaesthesia *8*(3): 151 (1953).
34. Griffith, H. R. See item 4.
35. Little, D. M. & Sutton, G. C. Succinylcholine-Nitrous Oxide Anaesthesia for Mitral Commissurotomy. Can. Anaesth. Soc. J. *2*(2): 156 (1955).
36. Paton, W. D. M. See item 33.
37. Winterbottom, H. E. Insufficient Anaesthesia. Letter to Editor, Brit. Med. J. *1*: 247 (1950).
38. Semelka, G. Personal communication.
39. Pittinger, C. B. & Morris, L. E. Observations of the Placental Transmission of Gallamine Triethiodide (Flaxedil), Succinylcholine Chloride (Anectine), and Decamethonium Bromide (Syndurine) in dogs. Anesth. & Anal. *34*(2): 107 (1955).

40. STEAD, A. L. The Response of the Newborn Infant to Muscle Relaxants. Brit. J. Anaes. *27*(3): 124 (1955).
41. DENNIS, J. W. & CARROLL, J. J. The Use of Short Acting Muscle Relaxing Drugs in Obstetrical Anaesthesia. Can. Anaes. Soc. J. *1*(2): 82 (1954).
42. FOLDES, F. F. *et al.* See item 11.
43. GUERRIER, S. M. & HUXLEY WILLIAMS, R. "Mixed" Scholine Block Reversed by Prostigmine. Correspondence, Anaesthesia *9*(3): 213 (1954).
44. ANDERSON, H. J., CHURCHILL-DAVIDSON, H. C. & RICHARDSON, A. T. Bronchial Neoplasm with Myasthenia: Prolonged Apnoea after Administration of Succinylcholine. Lancet 2: 1291 (1953).
45. ARGENT, D. E., DINNICK, O. P. & HOBBINGER, F. Prolonged Apnoea after Suxamethonium in Man. Brit. J. Anaes. *27*(1): 24 (1955).
46. COWAN, K. A. Nine Hours' Apnoea following Succinylcholine. Anaesthesia *9*(1): 23 (1954).
47. LOVE, S. H. S. Prolonged Apnoea following Scholine. Correspondence, Anaesthesia *7*(2): 113 (1952).
48. CALVERT, J., LEHMANN, H., SILK, E. & SLACK, W. K. Prolonged Apnoea after Suxamethonium. Lancet 2: 354 (1954).
49. WOLFERS, P. Sensitivity to Succinylcholine Chloride. Letter to Editor, Brit. Med. J. 2: 162 (1952).
50. HURLEY, M. J. & MONRO, A. B. Prolonged Respiratory Paralysis after Succinylcholine. Letter to Editor, Brit. Med. J. *1*: 1027 (1952).
51. DAY, B. L. Prolonged Respiratory Paralysis after Succinylcholine. Letter to Editor, Brit. Med. J. 2: 162 (1952).
52. REID, J. E. & NEILL, D. W. Succinylcholine. Letter to Editor, Lancet 2: 639 (1952).
53. LANGTON HEWER, C. Prolonged Respiratory Paralysis after Succinylcholine. Letter to Editor, Brit. Med. J. *1*: 971 (1952).
54. KENNEDY-HARPER, J. Prolonged Respiratory Paralysis after Succinylcholine. Letter to Editor, Brit. Med. J. *1*: 865 (1952).
55. BOURNE, J. G. Long Action of Suxamethonium (Succinylcholine) Chloride. Brit. J. Anaes. *25*(2): 116 (1953).
56. MARTIN, R. C. *et al.* See item 14.
57. FOLDES, F. F. Prolonged Respiratory Paralysis after Succinylcholine. Letter to Editor, Brit. J. Anaes. *1*: 1352 (1952).
58. ELLIS, C. H., NORTON, S. & MORGAN, W. V. Central Depression by Drugs which Block Neuromuscular Transmission. Fed. Proc. *11*: 42–43 (1952).
59. LEE, J. A. A Synopsis of Anaesthesia. 3rd ed., Bristol: John Wright and Sons Ltd. (1953).
60. EVANS, F. T., GRAY, P. W. S., LEHMANN, H. & SILK, E. Sensitivity to Succinylcholine in relation to Serum-Cholinesterase. Lancet *1*: 1229 (1952).
61. HODGES, R. J. H. & HARKNESS, J. Suxamethonium Sensitivity in Health and Disease. Brit. Med. J. 2: 18 (1954).
62. SRINIVASAN, P. R. & PATWARDHAN, V. N. Plasma-Esterase and Plasma-Lipase Levels in Nutritional Oedema Syndrome (Kwashiorkor). Lancet 2: 864 (1952).
63. SMITH, L. D. & VIRTUE, R. W. Succinylcholine: A Case Report and Experimental Study. Anesthesiology *15*(1): 42, 1954.
64. DE CLIVE-LOWE, S. G., GRAY, P. W. S. & NORTH, J. Succinylcholine and Lignocaine by Continuous Intravenous Drip. Anaesthesia *9*(2): 96 (1954).
65. CALVERT, J., LEHMANN, H., SILK, E. & SLACK, W. K. See item 48.
66. FORBAT, A., LEHMANN, H. & SILK, E. Prolonged Apnoea following Injection of Succinyldicholine. Lancet 2: 1067 (1953).
67. CALLAWAY, S., DAVIES, D. R. & RUTLAND, J. P. Blood Cholinesterase Levels and Range of Personal Variation in a Healthy Adult Population. Brit. Med. J. 2: 812 (1951).
68. MCARDLE, B. Estimation of Cholinesterases. Quart. J. Med. 33: 107 (1940).
69. HINK, J. H. Measuring Cholinesterase Activity. Letter to Editor, Lancet 2: 455 (1953).

70. Lehmann, H. Succinylcholine. Letter to Editor, Lancet *2*: 199 (1952).
71. Harrison, B. L., Seward, E. H. & Skinner, L. C. Prolonged "Scoline" Apnoea Treated by Blood Transfusion. Anaesthesia 9(1): 21 (1954).
72. Evans, F. T., Gray, P. W. S., Lehmann, H. & Silk, E. Effect of Pseudocholinesterase Level on Action of Succinylcholine in Man. Brit. Med. J. *1*: 136 (1953).
73. Hink, J. H., Jr. Personal communication.
74. Argent, D. E. *et al.* See item 45.
75. Guerrier, S. M. *et al.* See item 43.
76. Ruddel, J. S. Succinylcholine. Letter to Editor, Lancet 2: 341 (1952).
77. Anderson, H. J. *et al.* See item 44.
78. Paton, W. D. M. See item 33.
79. Hunter, A. R. The Classification of the Myoneural Blocking Agents. Brit. J. Anaes. 27(6): 399 (1954).
80. Grant, G. Prolonged Respiratory Paralysis after Succinylcholine. Letter to Editor, Brit. Med. J. *1*: 1352 (1952).
81. Forrester, A. T. T. Treatment of Tetanus with Succinylcholine. Brit. Med. J. 2: 342 (1954).
82. Scurr, C. F. Carbon Dioxide Retention Simulating Curarization. Brit. Med. J. *1*: 564 (1954).
83. Borders, R. W., Stephen, C. R., Nowill, W. K. & Martin, R. The Interrelationship of Succinylcholine and the Blood Cholinesterases during Anesthesia. Anesthesiology *16*(3): 401 (1955).
84. Davis, D. A., Ellis, F. C., Reese, N. O. & Grosskreutz, C. D. The Prolonged Effects of Succinylcholine and Some Possible Explanations for These Phenomena. Anesthesiology *16*(3): 333 (1955).

THE RELATION OF PLASMA CHOLINESTERASES TO RESPONSE TO CLINICAL DOSES OF SUCCINYLCHOLINE*

WERNER KALOW, M.D.**

MANY MUSCULAR RELAXANTS have been introduced during the past decade. Of all these relaxants, succinylcholine is the only drug with a fleeting action. This short duration of action has been ascribed to a rapid enzymatic destruction of succinylcholine in the body (1, 2).

The only enzyme which is known to destroy succinylcholine in man is plasma cholinesterase. There are several synonyms for plasma cholinesterase. The enzyme is also called serum cholinesterase, pseudo-cholinesterase, or non-specific cholinesterase. The enzyme is distinctly different from acetyl-cholinesterase (or true cholinesterase) (3), which destroys acetylcholine *in vivo* and which is essential for various functions of the nervous system (4). Plasma cholinesterase is secreted by the liver into the blood (5), but its purpose is unknown. Besides being present in plasma and serum, this esterase occurs in various tissues (6), for instance in pancreas (7) and in the white matter of the human brain (8). Plasma cholinesterase differs in its behaviour from species to species (9), and it does not occur in the plasma of all mammals (10).

We shall first consider the enzymatic destruction of succinylcholine *in vitro*. The enzymatic deactivation of succinylcholine is a hydrolysis and proceeds in two steps (11, 12). First, succinyldicholine is split into succinylmonocholine and choline. Succinylmonocholine is roughly one-twentieth as active in man as succinyldicholine (13, 14). In the second step, which is a separate reaction, succinylmonocholine is split into succinic acid and choline.

Either succinyldicholine or succinylmonocholine combines with the esterase, and during this combination choline is split off. The combining power between enzyme and drug (15) is, therefore, an important measure but it is sufficient at the moment to state that the apparent affinity[1] between succinyldicholine and plasma cholinesterase is twenty times greater than the apparent affinity between succinylmonocholine and the enzyme (16). This is one of the reasons why the reaction occurs in two steps. Figuratively speaking, if the enzyme has a free choice between succinyldicholine and succinylmonocholine, it prefers succinyldicholine. However, the enzyme does not always have a free choice.

The rate of the enzymatic reaction depends on the following three factors: first, the intrinsic speed; second, the concentration of succinylcholine; third, the concentration of the esterase. We have to consider these three factors one by one.

First, there is the intrinsic speed with which the enzyme can handle succinylcholine. This is expressed as a maximum rate of reaction and we state this as

*Presented at the Annual Meeting of the Canadian Anaesthetists' Society, Toronto, June 20, 1955.

**Department of Pharmacology, University of Toronto.

[1]I.e., the reciprocal of the Michaelis constant. The constants were reported (16) as 1.3×10^{-3} for succinyldicholine and 2.6×10^{-2} for succinylmonocholine.

follows. A normal adult has about 3½ litres of plasma. If these 3½ litres have an average esterase activity, they are capable of hydrolysing either 120 mg. of succinyldicholine chloride per minute (17), or 60 mg. of succinylmonocholine chloride per minute. Thus, at maximum rates the first step of the reaction between plasma cholinesterase and succinylcholine is twice as fast as the second step (16).

Second, the concentrations of succinyldicholine (16, 17) and succinylmonocholine (16) influence the rate of reaction. The maximum speed of destruction of succinyldicholine is obtained only if the enzyme is saturated with succinyldicholine, that is, at high concentrations of succinyldicholine. If the concentration of succinyldicholine is low, the rate of reaction is slow. The more its concentration rises, the faster it is destroyed until at very high concentrations the maximum rate is reached. The same rule holds for succinylmonocholine.

One cannot make a general statement saying that the first step of the hydrolysis is faster than the second step. The ratio of reaction velocities depends on the concentrations of the two compounds. If the concentration of succinylmonocholine is very high and the concentration of succinyldicholine very low, then succinylmonocholine would be hydrolysed faster. Therefore, there must be concentrations where succinyldicholine and succinylmonocholine are hydrolysed at the same rate, when both are simultaneously exposed to the esterase. A calculation shows that the first and the second steps of the reaction must be equally fast if the concentration of succinylmonocholine exceeds forty times the concentration of succinyldicholine.[2] Or vice versa, if they are hydrolysed at the same rate, the ratio of concentrations is always 1 to 40 regardless of the actual concentration of succinyldicholine. This is a key figure for our later deductions.

Third, the rate of reaction is influenced by the concentration of the enzyme, which is often called the plasma level of cholinesterase. The rate of reaction is proportional to the concentration of esterase (17); thus, doubling the esterase level causes the reaction to proceed twice as fast. It is important to notice that this rule also holds at low concentrations of succinylcholine when the reaction rate is slow.

The significance of these enzymological data can now be discussed. There is no reason to assume that the enzyme acts differently towards succinylcholine *in vivo* than it does *in vitro*. Thus the circulating plasma cholinesterase of the normal adult could destroy up to 120 mg. of succinylcholine chloride per minute. We can conclude that the plasma cholinesterase is an important factor for the deactivation of succinylcholine in the human body.

[2]The equation for competitive inhibition is frequently described in the enzymological literature (e.g., F. M. Huennekens in *Technique of Organic Chemistry*, vol. VIII, edited by A. Weissberger [New York: Interscience Publishers Inc., 1953], Equation 41, p. 572 and equation 65, p. 586). For our calculation this equation was first written treating succinyldicholine as the substrate and succinylmonocholine as the inhibitor. Thus, the first equation describes the rate of hydrolysis of succinyldicholine. The second equation was set up treating succinyldicholine as the inhibitor, and calculating the rate of hydrolysis of the substrate succinylmonocholine. If both these rates of hydrolysis are equal, the first and second equations can be combined to form a third equation. By inserting numerical values for the Michaelis constants and the maximum velocity into the third equation, the above mentioned ratio of concentrations was obtained.

One can never reach the concentration of succinyldicholine in the circulating blood that would saturate the esterase and cause a maximum reaction rate. The esterase would act at only half the maximum rate if 1 to 2 gm. of succinylcholine were in the circulating plasma, and, also, this concentration is far in excess of practical limits. It follows that only a fraction of the available esterase can be active at any given time. We do not yet know the blood level of succinylcholine after injection, owing to the chemical difficulties of such a determination. We are, therefore, not sure how fast the circulating plasma cholinesterase acts *in vivo*, and whether we must expect that other factors contribute to the destruction of succinylcholine, such as the liver esterase. It has been found, however, that hardly any succinylcholine appears in the urine (18).

Although only a fraction of the available plasma cholinesterase will be occupied at any given moment by succinylcholine *in vivo*, the size of this fraction is proportional to the esterase level. In other words, the esterase does not act at its full capacity whether its level is high or low.

If one gives a slow constant intravenous drip of succinylcholine over long periods of time, a certain degree of relaxation will be achieved and maintained as long as the drip lasts (19). That means, the drip brings the plasma concentration of succinyldicholine to such a level that the esterase acts at a rate whereby just as much is destroyed per minute as one puts into the system. If the rate of drip is increased, the blood level will be higher, which causes the esterase to act faster, and a new equilibrium will be established. In other words, the blood level adjusts itself so that input and destruction are balanced.

This equilibrium must be maintained also for succinylmonocholine. The concentration of succinylmonocholine shortly after the start of the drip is very low so that it is destroyed very slowly, its concentration builds up, and correspondingly the destruction of succinylmonocholine becomes faster. Ultimately it will reach a level of concentration where its rate of formation is just as fast as its rate of destruction; in other words, succinylmonocholine will be removed just as fast as succinyldicholine is injected and destroyed. If the plasma cholinesterase is the only deactivating force, it follows that at equilibrium the plasma concentration of succinylmonocholine must be forty times as high as the concentration of succinyldicholine. Thus, from our present knowledge of the interaction between plasma cholinesterase and succinylcholine, we must predict that during slow intravenous infusion succinylmonocholine regularly accumulates.

When sufficient succinyldicholine was administered to achieve relaxation of momentary duration, succinylmonocholine could not possibly reach an effective level. Between these two extremes of rapid injection and prolonged drip, all intermediate stages of accumulation of succinylmonocholine must be expected to occur.

No matter how effectively the plasma cholinesterase can attack succinylcholine in the blood, the drug in the body is not always exposed to the esterase. Very shortly after intravenous injection, a major portion of succinylcholine must have left the blood vessels to be distributed over the extracellular space. Figure 1 explains this conclusion. It shows a schematic cross-section of single muscle fibres and capillaries in between. A motor nerve with its end-plate is shown

supplying one of the muscle fibres. After intravenous injection, the drug is carried by the blood into the capillaries. In order to reach the end-plate, the site of action of succinylcholine, the drug has to leave the capillaries and it must diffuse through the extracellular space. As is known from the rapid onset of action of succinylcholine, these processes of crossing the capillary walls and travelling through the extracellular space towards the end-plate must occur with great speed. The main driving force for these processes is probably the concentration gradient. The extracellular space outside the blood vessels is roughly three times as large as the blood volume. Thus, within a short time there must be more succinylcholine outside the blood than inside.

It is not very likely that the normal extracellular fluid contains much plasma cholinesterase. Ascitic fluid (20) and cerebrospinal fluid (21) have been shown

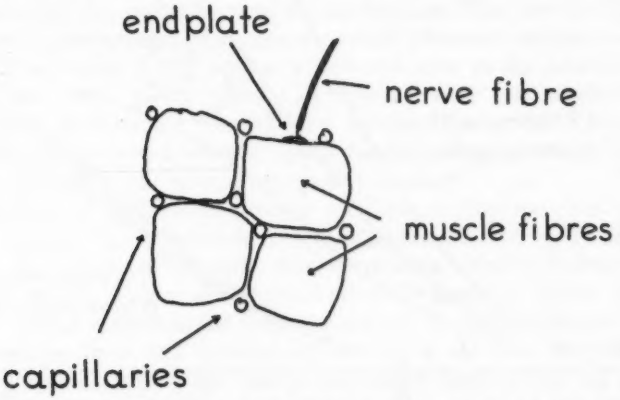

FIGURE 1. Schematic cross-section through single muscle fibres and capillaries. This figure demonstrates that a drug must leave the vascular bed and enter the extracellular fluid before it can reach the end-plate. Since the extravascular space is larger than the vascular bed, the drug becomes diluted and more of it must be outside the capillaries than inside. The figure was drawn after consultation with Dr. S. Bensley of the Department of Anatomy, University of Toronto.

to contain some, but very little, esterase. Thus, shortly after intravenous injection, a considerable portion of succinylcholine is in the extracellular space and thereby out of reach of the circulating esterase. In other words, the esterase guards the entrance to and the exit from the tissues but the esterase cannot be blamed for irregularities which might occur in the tissues, at the site of action of succinylcholine.

The foregoing theoretical deductions fit the following clinical experiences. First, the importance of the enzyme for the deactivation of succinylcholine has been confirmed by several observations. There are numerous reports of cases with a low esterase level where a prolonged apnoea after succinylcholine occurred (2, 22, 23, 24, 25, 26, 27, 28).

We can add here the description of some particularly instructive cases which were observed in Toronto. We had the opportunity to study three sera with

extremely low esterase activity from patients who had reacted with prolonged apnoea after succinylcholine.

On repeated routine investigations these sera showed an esterase activity between 30 and 50 units; the average plasma contains 210 units. To our surprise, these esterases showed some unusual behaviour in addition to their low activity. (Figure 2 gives an example.) The activity was not equally reduced towards

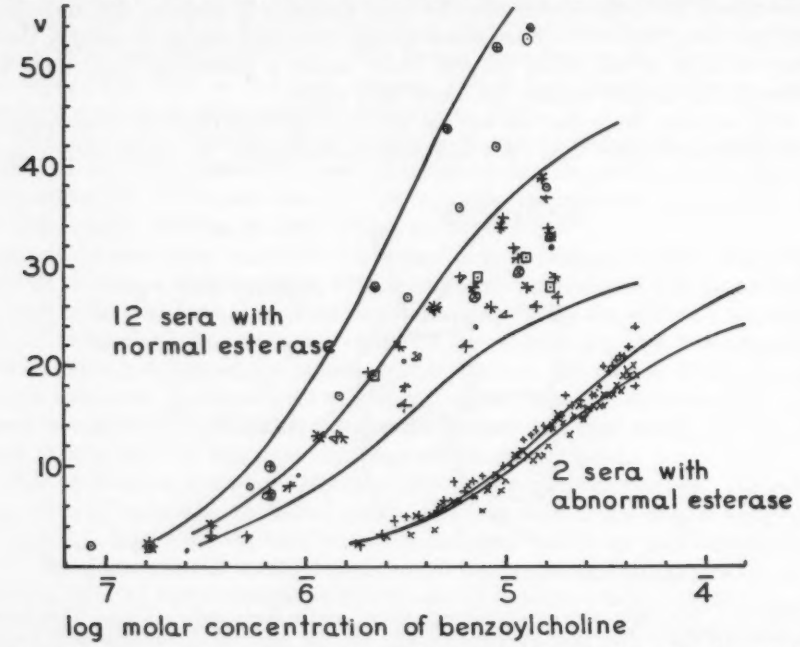

FIGURE 2. A contrast between normal and abnormal behaviour of human plasmacholinesterase. The rate of hydrolysis of benzoylcholine (determined by ultraviolet spectrophotometry) is plotted against log concentration of benzoylcholine. Experiments on different sera are designated by different symbols. The common type of variation between different sera causes the S-shaped curves to be more or less steep. The two abnormal curves are shifted horizontally. The abnormality has persisted for more than a year and is not confined to benzoylcholine. The hydrolysis of succinylcholine is not measurable. The presence of an unknown competitive inhibitor is excluded by dialyzing experiments.

various cholinesters, affinities were lower, and they were not so easily inhibited (for instance, by neostigmine). There were no signs of an unknown inhibitor. In short, there were changes which are hard to explain at the moment and which indicated a deeply distorted as well as a low esterase activity. Direct measurements revealed that these esterases split succinylcholine so slowly that no accurate data were obtained.[3]

One of these patients was anaesthetized by Dr. MacKay at the Toronto General Hospital. The patient was 6 feet tall, weighed 180 pounds, and was in good

[3]The enzymatic hydrolysis in the Warburg apparatus was considerably slower than the spontaneous hydrolysis of succinylcholine.

health except for a minor surgical condition. He was totally apnoeic for almost three-quarters of an hour after the injection of 40 mg. of succinylcholine iodide. Consciousness returned before respiration. Two sera were from mental patients of Dr. Gunn from the Ontario Hospital, New Toronto. They were given succinylcholine repeatedly for electroshock treatment and Dr. Gunn used these occasions to determine the optimal dose. One of these patients required only 5 mg. of succinylcholine chloride for adequate relaxation but the apnoea lasted for 8 to 15 minutes. Ten mg. caused apnoea for 22 to 25 minutes. The second patient required 10 mg. and the duration of apnoea was similar to that of the other patient, namely between 20 and 24 minutes. In these cases with extremely low esterase activity, succinylcholine acted almost as decamethonium acts in a normal person.

There are other types of evidence which demonstrate the importance of plasma cholinesterase for the metabolism of succinylcholine. The time of apnoea can be shortened by intravenous injection of purified plasma cholinesterase (28, 29, 30). The above holds, if the esterase is injected prior to the administration of succinylcholine (28). If the esterase is injected after the administration of succinylcholine, it does not terminate an existing apnoea (28). Under these circumstances, the injected esterase comes too late to guard the entrance into the tissues. Therefore, one cannot expect its full effect.

The injection of anti-cholinesterases, such as neostigmine, was repeatedly shown to increase the duration of action of succinylcholine (31, 32, 33, 34). Evans and co-workers (2) showed a close correlation between esterase level and duration of apnoea. Foldes and co-workers (35) found a partial correlation. Among the mental patients in the Ontario Hospital, Dr. Gunn finds no correlation between esterase level and duration of apnoea, if the few exceptional cases which were reported above are disregarded. Since there is also no correlation between dose of succinylcholine and duration of apnoea, one suspects that the electroshock itself can modify the duration of action of succinylcholine to a certain extent.

A second theoretical conclusion was that the esterase in the body is not acting at its maximum capacity; in other words, that there is a reserve of esterase activity which can be utilized if the plasma concentration of succinylcholine is very high. This is confirmed by some experiments of Dr. Gunn who, on several occasions, administered 1000 mg. of succinylcholine chloride by rapid intravenous injection. The apnoea lasted for only a few minutes even after this extremely high dose. The esterase activity in these patients was normal. Similar observations were made by Borders and his co-workers (28) during anaesthesia.

Third, it has been presented as a theoretical deduction that succinylmonocholine accumulates regularly during continuous infusions of succinyldicholine. The significance of this conclusion cannot be evaluated for several reasons. It is not known whether there are more effective means than the plasma cholinesterase for the detoxification of succinylmonocholine. Such factors could prevent the accumulation which the esterase would cause.

Although the esterase action permits a prediction of ratios of concentrations of the two succinylcholines, the absolute values of these concentrations are

unknown. Furthermore, it is not known what drop of the plasma levels is necessary to terminate the relaxant actions. Thus, one cannot calculate how long the effects will persist after the termination of a continuous infusion or intravenous injection.

It is known that roughly twenty times more succinylmonocholine than succinyldicholine is necessary to produce a desired clinical effect. In view of the possible accumulation of succinylmonocholine, however, the potency of succinylmonocholine relative to that of succinyldicholine at the human motor end-plate may be less than it appears to be from a study of intravenous injections.

Finally, we concluded that one cannot expect that all unusual reactions with succinylcholine are due to a low activity of plasma cholinesterase. During the past year, we have received several samples of normal plasma from patients with prolonged apnoea after succinylcholine. Prolonged apnoea has been reported after all muscular relaxants (36), and some factor may occasionally affect the action of succinylcholine which could also affect some other relaxant.

Summary

The plasma cholinesterase of a normal adult is capable of destroying *in vitro* up to 120 mg. per minute of succinylcholine chloride. This great speed of destruction cannot be obtained *in vivo*, yet the normal plasma cholinesterase can effectively cope with a considerable excess of succinylcholine.

The rate of destruction of succinylcholine for any given concentration of succinylcholine is proportional to the concentration of plasma cholinesterase.

On slow intravenous infusion of succinyldicholine, the plasma cholinesterase must be assumed always to cause an accumulation of succinylmonocholine so that the concentration of succinylmonocholine exceeds by about 40 times the concentration of succinyldicholine. It is not yet clear whether this accumulation of succinylmonocholine is prevented by factors other than plasma cholinesterase, or whether this accumulation escapes clinical detection.

In order to exert its action at the neuromuscular junction, succinylcholine must enter the extravascular space where it is not exposed to plasma cholinesterase. Thus one cannot expect the esterase to be responsible for all abnormal reactions towards succinylcholine.

The sera of three patients are described; in these cholinesterase activity towards succinylcholine is too low to be measured. In all three cases the esterase has some peculiarities which are not fully explained. In one of these patients injection of 5 mg. of succinylcholine chloride was found to cause profound relaxation and 15 minutes' apnoea.

Acknowledgments

I wish to take advantage of this occasion to say some words of thanks. Without stimulus from Professor J. K. W. Ferguson and Dr. R. A. Gordon this paper would not have been written. Dr. Gordon continued his help by sending samples of plasma and discussing his cases. Dr. F. F. Foldes of Pittsburgh assisted by sending his data when our supply of succinylmonocholine failed. All calculations involving succinylmonocholine are based on unpublished data by Dr. Foldes.

RÉSUMÉ

La plasma cholinestérase d'un adulte normal peut détruire *in vitro* jusqu'à 120 mg. per minute de chlorure de succinylcholine. *In vivo*, la réaction enzymatique n'est pas si rapide parce que la concentration plasmatique de la succinylcholine n'est pas assez élevée pour saturer l'enzyme. En d'autres mots, la plasma cholinestérase normale peut détruire plus de succinylcholine en peu de temps qu'il n'est nécessaire pour obtenir un effet de relâchement musculaire.

Pour une concentration donnée de succinylcholine, la vitesse de destruction doit être proportionnel au niveau plasmatique de la cholinestérase même si l'estérase n'agit pas à sa capacité maximum.

Lorsqu'une solution de succinyldicholine est injectée lentement en intraveineuse, on doit toujours se rappeler que la plasma cholinestérase cause une accumulation de succinylmonocholine de sorte que la concentration de succinylmonocholine est environ 40 fois celle de la succinyldicholine. On ne connait pas encore si cette accumulation de succinylmonocholine est arrêtée par d'autres facteurs que la plasma cholinestérase ou bien si elle échappe à l'investigation clinique.

La succinylcholine agit à la jonction neuro-musculaire. Pour l'atteindre, la succinylcholine doit entrer dans le milieu extra cellulaire. Dans le liquide extravasculaire la succinylcholine n'est pas au contact de la plasma cholinestérase. En d'autres mots, l'estérase previent l'entrée et la sorties dans les tissus mais ne peut être tenu responsable des irrégularités qui peuvent survenir dans les tissus au lieu d'action de la succinylcholine.

Il est connu que la concentration de plasma cholinestérase varie d'une personne à une autre. Habituellement il s'agit et une variation de quantité de l'enzyme mais il peut survenir aussi des variations dans les propriétés de la plasma cholinestérase. Seulement dans trois de ces cas, l'activité de l'estérase sur la succinylcholine fût trop basse pour être mesurer. Chez l'un de ces patients, l'injection de 5 mg. de succinylcholine causa un relâchement musculaire profond et une apnée de 15 minutes.

REFERENCES

1. Bovet-Nitti, F. Degradazione di Alcune Sostanze Curarizzanti per Azione di Colinesterasi. Rend. 1st Super. Sanita. *12*: 138 (1949).
2. Evans, F. T., Gray, P. W. S., Lehmann, H. & Silk, E. Sensitivity to Succinylcholine in relation to Serumcholinesterase. Lancet *1*: 1229 (1952).
3. Mendel, B. & Rudney, H. Studies on Cholinesterase; I, Cholinesterase and Pseudocholinesterase. Biochem. J. *37*: 59 (1943).
4. Wilson, I. B. & Cohen, M. The Essentiality of Acetylcholinesterase in Conduction. Biochim. et Biophys. Acta. *11*: 147 (1953).
5. Wilson, A., Calvert, R. J. & Geoghegan, H. Plasmacholinesterase Activity in Liver Disease: Its Value as a Diagnostic Test of Liver Function compared with Flocculation Tests and Plasma Protein Determinations. J. Clin. Investigation *31*: 815 (1952).
6. Whittaker, V. P. Mode of Action and Distribution of Cholinesterases. Physiol. Rev. *31*: 312 (1951).
7. Mendel, B. & Mundell, D. B. Studies on Cholinesterase; II, A Method for the Purification of a Pseudocholinesterase from Dog Pancreas. Biochem. J. *37*: 64 (1943).
8. Ord, M. G. & Thompson, R. H. S. Pseudocholinesterase Activity in the Central Nervous System. Biochem. J. *51*: 245 (1952).

9. Myers, D. K. Studies on Cholinesterase; IX, Species Variation in the Specificity Pattern of the Pseudocholinesterases. Biochem. J. *55*: 67 (1953).
10. Mendel, B., Mundell, D. B. & Rudney, H. Studies on Cholinesterase; III, Specific Tests for True Cholinesterase and Pseudocholinesterase. Biochem. J. *37*: 473 (1943).
11. Whittaker, V. P. & Wijesundera, S. Hydrolysis of Succinylcholine by Cholinesterase. Biochem. J. *52*: 475 (1952).
12. Tsuji, F. I. & Foldes, F. F. Hydrolysis of Succinylcholine in Human Plasma. Fed. Proc. *12*: 374 (1953).
13. Foldes, F. F., McNall, P. G. & Birch, J. H. The Neuromuscular Activity of Succinylmonocholine Iodide in Anaesthetized Man. Brit. Med. J. *1*: 967 (1954).
14. Foldes, F. F., Vandervort, R. S. & Shanor, S. P. The Fate of Succinylcholine in Man. Anesthesiology *16*: 11 (1955).
15. Michaelis, L. & Menten, M. I. Die Kinetic der Invertinwirkung. Biochem. Zschr. *49*: 333 (1913).
16. Foldes, F. F. Personal communication.
17. Lindsay, H. A. & Kalow, W. To be published.
18. Foldes, F. F. & Norton, S. T. The Urinary Excretion of Succinyldicholine and Succinylmonocholine in Man. Brit. J. Pharmacol. *9*: 385 (1954).
19. Espinosa, A. M. & Artusio, J. F. The Dose Response Relationship and Duration of Action of Succinylcholine in Anaesthetized Man. Anesthesiology *15*: 239 (1954).
20. Fremont-Smith, K., Volwiler, W. & Wood, P. A. Serum Acetylcholinesterase, Its Close Correlation with Serum Albumin, and Its Limited Usefulness as a Test of Liver Function. J. Lab. Clin. Med. *40*: 692 (1952).
21. Colling, K. G. & Rossiter, R. J. Cholinesterases of Cerebrospinal Fluid. Can. J. Res., Sect. E. *27*: 327 (1949).
22. Bourne, J. G., Collier, H. O. J. & Somers, G. F. Succinylcholine (Succinoylcholine) Muscle Relaxant of Short Action. Lancet *1*: 1225 (1952).
23. Evans, F. T., Gray, P. W. S., Lehmann, H. & Silk, E. Succinylcholine. Lancet *2*: 682 (1952).
24. Reid, J. E. & Neill, D. W. Succinylcholine Apnoea. Lancet 2: 1232 (1952).
25. Forbat, A., Lehmann, H. & Silk, E. Prolonged Apnoea following Injection of Succinyldicholine. Lancet 2: 1067 (1953).
26. Calvert, J., Lehmann, H., Silk, E. & Slack, W. K. Prolonged Apnoea after Suxamethonium. Lancet 2: 354 (1954).
27. Bourne, J. G. Succinylcholine. Lancet 2: 495 (1954).
28. Borders, R. W., Stephen, C. R., Nowill, W. K. & Martin, R. The Interrelationship of Succinylcholine and the Blood Cholinesterases during Anesthesia. Anesthesiology *16*: 401 (1955).
29. Evans, F. T., Gray, P. W. S., Lehmann, H. & Silk, E. Effect of Pseudocholinesterase Level on Action of Succinylcholine in Man. Brit. Med. J. *1*: 136 (1953).
30. Paton, W. D. M. Principles of Neuromuscular Block. Anaesthesia *8*: 151 (1953).
31. Castillo, J. C. & de Beer, E. J. Neuromuscular Blocking Action of Succinylcholine (Diacetylcholine). J. Pharmacol. & Exper. Therap. *99*: 458 (1950).
32. Bovet, D., Bovet-Nitti, F., Guarino, S., Longo, V. G. & Fusco, R. Synthetic Curarizing Agents; III, Succinylcholine and its Aliphatic Derivatives. Arch. internat. de Pharmacodyn. et de therap. *88*: 1 (1951).
33. Low, H. & Tanimelin, E. Succinylcholine, a Neuromuscular Blocking Drug, and its Synergism with Tetraethylpyrophosphate. Acta Physiol. Scand. *23*: 78 (1951).
34. Lucas, B. G. B. & Miles, S. Anticholinesterases and Muscle Relaxants. Brit. Med. J. *1*: 579 (1955).
35. Foldes, F. F., Swerdlow, M., Lipschitz, E. & van Hees, G. Comparison of Enzymatic Hydrolysis of Suxamethonium and Suxethonium with their Respiratory Effects. Fed. Proc. *14*: 339 (1955).
36. Dripps, R. D. Abnormal Respiratory Response to Various "Curare" Drugs during Surgical Anesthesia: Incidence, Etiology, and Treatment. Ann. Surg. *137*: 145 (1953).

PLASMA CHOLINESTERASE STUDIES IN SOME PATHOLOGICAL CONDITIONS IN MAN

W. A. Wielhorski, M.B., Ch.B.,* M. Dubeau, M.D.,* and P. Riopel, M.Sc., M.C.I.C.**

In the last few years, there has been a growing interest in plasma cholinesterase. Until recently, study of this subject has been mostly confined to physiological and biochemical laboratories. The discovery of organic phosphorous ester-type war gases, the introduction of anti-cholinesterase substances, such as insecticides in agriculture, and the recent use of succinylcholine as a relaxant in anaesthesia—all these events have made the knowledge of cholinesterase properties of very practical value (1, 2).

Cholinesterases are enzymes widely distributed in animal tissues. They catalyse the hydrolysis of acetylcholine. Two types of this enzyme have been described and can be identified by chemical tests (3, 4): the specific cholinesterase of tissues and red cells, and the non-specific cholinesterase in the plasma also called pseudo-cholinesterase.

There is now little doubt as to the physiological role of the specific acetylcholinesterase which is bound to the cell membranes; its function seems to be ultra-rapid inactivation of free acetylcholine. This reaction is essential for the development and propagation of the action potential and for the metabolism of all nerve cells (5). The importance of this enzyme for normal life has been demonstrated clearly by the fact that selective inhibition of its activity by organic phosphorous ester-type war gases is very rapidly fatal to man and other animals.

On the other hand, there is practically nothing known about the physiological role of the non-specific cholinesterase which is present mainly in the plasma. No substrate has been found equivalent to acetylcholine which would explain the presence in plasma of this highly active and potent esterase. Selective poisoning of plasma cholinesterase by D.F.P. (di-isopropyl fluoro-phosphate) injections in experimental animals and in man has not been fatal even when the enzyme activity was reduced to zero (18). This is in sharp contrast to the effect of complete inactivation of true cholinesterase, which is rapidly fatal.

In spite of the apparent lack of importance and the surrounding mystery of its function, we have been interested in plasma cholinesterase because it has been demonstrated to hydrolyse succinylcholine *in vitro* and *in vivo* (2). Studies of the behaviour of cholinesterase in the plasma might be of some use to us if we have to depend on its activity in our daily anaesthetic practice (6, 7).

Methods of Estimating Cholinesterase

All chemical methods depend upon measurement of the acid produced by the action of cholinesterase on acetylcholine. We have been using the electrometric method of Michel (12). The drop in pH resulting from the liberation of acetic acid, when acetylcholine is hydrolysed, is measured with a glass electrode at

*Department of Anaesthesiology, Maisonneuve Hospital, Montreal.
**Department of Biochemistry, Maisonneuve Hospital, Montreal.

25°C. The result is then corrected for non-enzymatic hydrolysis by the use of Michel's tables and the plasma cholinesterase activity is expressed in units of decrease of pH per hour (ΔpH/hour). Other methods used to estimate esterase level are: titrimetric technique of Willstatter *et al.* (8); gasometric method of Ammon (9) or McArdle (19); photometric method of Croxatto (10); colorimetric method of Ravin (11); biological estimations of Hicks and MacKay (20).

Normal Values of Cholinesterase Activity

Callaway *et al.* (15) determined cholinesterase in 247 healthy adults in England and found the plasma cholinesterase to be between 57 and 143 per cent of the mean value. They found no sex, age, or seasonal differences.

Vorhaus and Kark (14) in 120 healthy individuals found a normal range for serum cholinesterase to be from 0.62 to 1.26 units. They found no correlation between the enzyme activity and age, sex, weight, height, or surface area. There were neither diurnal nor seasonal fluctuations.

In spite of a wide range of normal values, all investigators confirmed that individuals have a very constant normal level which does not vary in health. For that reason, interpretation of single measurements may often be difficult, but repeated tests have been found of great service to follow the degree of recovery from organo-phosphorous poisoning (22).

Deviations from Normal Plasma Cholinesterase Values

Several investigators attempted to correlate plasma cholinesterase activity with various pathological conditions. The most constant finding was a reduction of cholinesterase in liver disease (17) and an increase in nephrosis (14). A close correlation exists between plasma levels of albumin and cholinesterase (23). The lower cholinesterase activity in liver diseases is probably due to impaired hepatic synthesis of this substance and, for that reason, cholinesterase estimations were recommended as a very sensitive liver function test (24, 21, 14).

Our main interest has been to try and estimate to what extent cholinesterase activity is reduced in liver disease and how patients with hepatic pathology react to succinylcholine infusion.

The investigations of Vorhaus and Kark (14) demonstrated that patients with obstructive jaundice have an enzyme activity within normal limits; those with acute hepatic conditions such as virus hepatitis or ascending cholangeitis have moderately depressed cholinesterase, and those with chronic liver diseases with marked hepatic tissue damage, such as occurs in cirrhosis, have the lowest cholinesterase values.

Case Histories

Our diagram shows the cases of five patients with low cholinesterase activity who made an uneventful recovery from succinylcholine continuous infusion during the operation.

Case No. 1. A man, 42 years of age, 150 pounds, diagnosed as having advanced cirrhosis of the liver. Plasma cholinesterase had been estimated preoperatively and found to be within the lower range of normal values, 0.66 units. Liver biopsy was

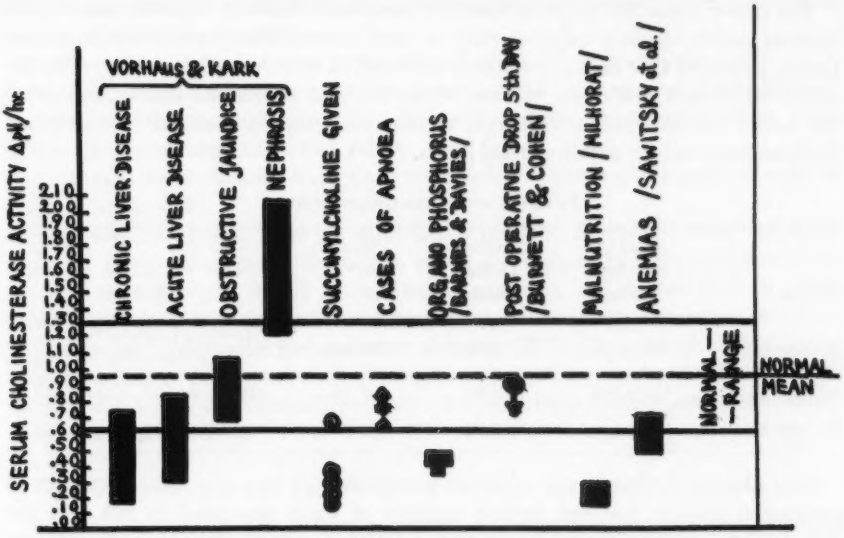

FIGURE 1. Deviations from normal plasma cholinesterase activity in various clinical circumstances.

performed under general anaesthesia with thiopentone, nitrous oxide, oxygen and an infusion of succinylcholine 0.15 per cent. A total of 150 mgm. of this relaxant were used during the surgical procedure which lasted one hour. On extubation, the patient showed complete recovery of muscular power.

Case No. 2. A 40-year-old female, 120 pounds, with obstructive jaundice, was found to have cholinesterase activity of 0.36 units. During a three-hour operation under nitrous oxide and oxygen anaesthesia, she received 150 mgm. of succinylcholine at a rate of 0.8 mgm. per minute, with normal recovery from the effects of this relaxant. Biopsy of the liver confirmed the diagnosis of advanced cirrhosis.

Case No. 3. A man, 35 years old, 135 pounds, with advanced cirrhosis of the liver and a cholinesterase activity of 0.34 units, had a liver biopsy performed under general anaesthesia. Over a period of 45 minutes, a total of 100 mgm. of succinylcholine were used as an adjuvant to thiopentone and nitrous oxide anaesthesia, at a rate of 2.2 mgm. per minute. Recovery was prompt and uneventful.

Case No. 4. This man, 44 years of age, 122 pounds, with suspected advanced homologous serum hepatitis, had an exploration of the common bile duct under general anaesthesia, his serum cholinesterase being at the level of 0.60 units. During a three and a half hour operation, 500 mgm. of succinylcholine were used with nitrous oxide and oxygen anaesthesia. A month later, one day prior to his death from hepatic failure, his plasma cholinesterase activity was still at the level of 0.26 units.

Case No. 5. Terminal liver failure in a 55-year-old man, 165 pounds, necessitated a laparotomy of 40 minutes' duration. With a cholinesterase activity of 0.20 units, he received, during the whole procedure, 50 mgm. of succinylcholine, recovery from anaesthesia being uneventful.

The above cases led us to believe that, even in advanced hepatic failure, continuous succinylcholine infusion may be used for obtaining relaxation in anaesthesia, provided due care is exercised to avoid an overdose. In contrast with the above-mentioned five cases, we had three cases of prolonged apnoea following the use of succinylcholine although, as shown on the diagram, all of them had cholinesterase values within normal limits.

PATIENTS WITH PROLONGED APNOEA

Patient	Dose of succinyl-choline	Cholines-terase (units)	Duration of apnoea	Remarks
A. Age 29	60 mgm.	0.86	40 min.	Technical difficulties with controlled respiration
B. Age 48	40 mgm.	0.80	60 min.	Deficient CO_2 elimination
C. Age 51	40 mgm.	0.63	60 min.	Deficient CO_2 elimination

Low plasma cholinesterase might be a contributing factor in some instances of prolonged apnoea, but our limited number of cases appeared to fall into the group where carbon dioxide retention could be suspected as the main factor producing symptoms of curarization as described by Scurr (25) and others (26, 27, 34). Gesell and Hansen (28) have demonstrated that carbon dioxide decreases the rate of destruction of acetylcholine by cholinesterase, but it is not yet known if this anti-cholinesterase action of carbon dioxide is strong enough to be of clinical significance in man.

EFFECT OF ORGANO-PHOSPHORUS INSECTICIDES ON PLASMA CHOLINESTERASE

Warnings against the use of succinylcholine in cases where there is history of exposure to this type of pesticides have been issued. Barnes and Davies (22) found reduced cholinesterase levels only in twelve workers out of eighty exposed to this type of chemical. Plasma cholinesterase level was found to be between 44 and 49 units, just below the normal values of 51 to 127 units according to their method. We had only one patient with a history of recent exposure to this type of insecticides and his preoperative cholinesterase level was 0.42 units. During a two-hour operation for cholecystectomy, he received 150 mgm. of succinylcholine, with a prompt and uneventful recovery.

CAUSES OF DEPRESSION OF PLASMA CHOLINESTERASE

Burnett and Cohen (24) reported a reduced plasma cholinesterase activity following operative procedures, which was most marked on the fifth postoperative day. As shown on our diagram, this reduction appears to be small, but in cases where the preoperative level is already low, it may become an additional factor tending towards cholinesterase insufficiency if and when a second operation has to be performed within a few days following the first one.

Malnutrition. Milhorat (42) has found very low values in patients with extreme cachexia and debilitation. The esterase activity in this type of patient was one-

fifth to one-tenth of normal. Such a low range is equivalent to that found in extreme cases of hepatic failure.

Prolonged fasting was found to be without effect on cholinesterase (42).

Reduced cholinesterase activity has been reported in cases of *schizophrenia, epilepsy,* and *catatonis stupor* (31). For schizophrenics, our estimations were within the lower range of normal values.

Acute infectious diseases have been reported to depress cholinesterase only to a slight extent. (14).

Anaemias. In various types of anaemias, a reduced esterase activity has been reported (29), although the reduction is not as great as in hepatic failure. The lowest readings were found in pernicious anaemia, in relapse and in acute leukaemia.

Therapeutic irradiation and radiation sickness (30). This type of condition has been reported to produce a drop in cholinesterase; the report should be kept in mind if one has to anaesthetize patients who have been given preoperative deep X-ray therapy.

Effect of Drugs

The reversible depression of cholinesterase activity by *physostigmine* and *prostigmine* is well known. A permanent inhibition of the enzyme is effected by the *alkyl-fluoro-phosphates* which are used as insecticides (e.g., D.F.P.).

Most *anti-malarial drugs* are very effective inhibitors of plasma cholinesterase: paludrine, plasmoquin, quinidine and quinine are included in this group (32).

Intensive treatment with *Vitamin K analogues,* often started before operation, may slightly depress cholinesterase (33). In our cases, the drop was never more than 0.10 to 0.15 units.

Similar effect is obtained in some patients receiving *Vitamin B-1—Thiamin* (35) in preoperative intravenous infusions. The reduction of activity in our cases was up to 0.20 units. However the increase in plasma volume produced by intravenous administration of fluids with a vitamin B-1 content may be partly responsible for the drop in enzyme activity.

Atropine and *Scopolamine* (36), morphine and its derivatives (37), chloroform and ether (38), barbiturates (5), curare (5), and cyclopropane in clinical dosage, have no significant influence on cholinesterase (16, 39).

On the other hand, substances which have been found to increase cholinesterase activity include *folic acid* (40) and *Vitamin E* (41).

Summary and Conclusions

A review of pathological conditions and of specific drugs which may affect plasma cholinesterase in man has been made. Short of experimental D.F.P. injections, there appear to be very few instances where reduction of plasma cholinesterase would bring it to such low values as to become a contra-indication to the use of succinylcholine. However, cases of severe hepatic damage and cachectic states exhibit the lowest plasma cholinesterase levels and, for that reason, it would seem advisable to exercise extreme care in the use of this relaxant.

Three cases of prolonged apnoea following infusion of succinylcholine have been reported, none of them exhibiting any deviation from normal plasma cholinesterase levels.

Résumé

Les auteurs font allusion au rôle de la cholinestérase cellulaire par contraste avec la cholinestérase plasmatique ou pseudo-cholinestérase. Pour l'estimation de cette dernière, ils ont fait appel, entre autres, à la méthode électrométrique de Michel, basée sur la diminution de pH résultant de l'acide acétique libéré à l'occasion de l'hydrolyse de l'acétylcholine par la pseudo-cholinestérase.

Les valeurs normales, basées sur cette méthode, se chiffreraient de 0.62 à 1.26 unités.

Les estimés ont été faits en vue d'apprécier d'une part le rôle joué par la pseudo-cholinestérase dans l'hydrolyse de la succinylcholine employée comme adjuvant en anesthésie, et de déterminer d'autre part l'influence que peuvent exercer certains états pathologiques ou certains agents chimiques et médicamenteux sur le taux de pseudo-cholinestérase et, indirectement, sur l'intensité d'action de la succinylcholine aux doses cliniquement employées.

Le niveau de la pseudo-cholinestérase a été trouvé abaissé dans certains états pathologiques tels que l'insuffisance hépatique, l'empoisonnement par insecticides, la malnutrition, l'état post-opératoire, la schizophrénie, les anémies, etc. . . —et à la suite de l'emploi de substances médicamenteuses telles que prostigmine et physostigmine, vitamine B-1, etc. . . .

Les états s'accompagnant d'une baisse de pseudo-cholinestérase offrent-ils une sensibilité plus marquée à l'action de la succinylcholine? De l'opinion des auteurs, cette sensibilité, bien que présente, ne ferai pas la règle et une curarisation prolongée secondaire à l'emploi de succinylcholine serait plus spécifiquement imputable à une rétention de gaz carbonique. Un taux bas de pseudo-cholinestérase n'exclut donc pas l'emploi de succinylcholine, mais engage simplement à une plus grande prudence.

REFERENCES

1. Glick, D. Some Additional Observations on the Specificity of Cholinesterase. J. Biol. Chem. *137*: 357 (1941).
2. Evans, F. T., Gray, P. W. S., Lehmann, H., & Silk, E. Sensitivity to Succinylcholine in relation to Serum Cholinesterase. Lancet *1*: 1229 (1952).
3. Alles, G. A. & Hawes, R. C. J. Biol. Chem. *133*: 375 (1940).
4. Mendel, B. & Rudney, H. Studies on Cholinesterase; I, Cholinesterase and Pseudocholinesterase. Biochem. J. *37*: 59 (1943).
5. Augustinsson, K. B. Cholinesterase, a Study in Comparative Enzymology. Acta Physiol. Scand. *15*, Suppl. 52.
6. Foldes, F. F. & Rhodes, D. H. Role of Plasma Cholinesterase in Anesthesiology. Anesth. & Analg. *32*: 305 (1953).
7. Kalow, W. Hydrolysis of Local Anesthetics by Human Serum Cholinesterase. J. Pharmacol. & Exper. Therap. *104*: 122 (1952).

8. Willstatter, R., Kuhn, R., Lind, O. & Memmen, E. Ueber Hemmung der Leberesterase durch Ketocarbonsaureester. Ztschr. f. physiol. Chem. *167*: 303 (1927).
9. Ammon, R. Die fermentative Spaltung des Acetylcholins. Pfluger's Arch. f.d. ges. Physiol. 233: 486 (1934).
10. Croxatto, H., Croxatto, R. & Huidobro, F. New Photometric method for the Determination of Serum Cholinesterase. Acad. Biol. Univ. Chile *3*: 55 (1939).
11. Ravin, H. A., Tson, K. C., & Seligman, A. M. Colorimetric Estimation and Histochemical Demonstration of Serum Cholinesterase. J. Biol. Chem. *191*: 843 (1951).
12. Michel, H. O. An Electrometric Method for the Determination of Red Blood Cell and Plasma Cholinesterase Activity. J. Lab. & Clin. Med. 32: 1564 (1949).
13. Reinhold, J. G., Tourigny, L. G. & Yonan, V. L. Measurement of Serum Cholinesterase Activity by a Photometric Indicator Method, together with a Study of the Influence of Sex and Race. Am. J. Clin. Path. *23*: 645 (1953).
14. Vorhaus, L. J. & Kark, R. M. Serum Cholinesterase in Health and Disease. Amer. J. Med. *14*: 707 (1953).
15. Callaway, S., Davies, D. R. & Rutland, J. P. Blood Cholinesterase Levels and Range of Personal Variation in a Healthy Adult Population. Brit. Med. J. *2*: 812 (1951).
16. Borders, R. W., Stephen, C. R., Nowill, W. K. & Martin, R. The Interrelationship of Succinylcholine and the Blood Cholinesterases during Anesthesia. Anesthesiology *16*: 401 (1955).
17. Antopol, W., Tuchman, L. & Schifrin, A. Decreased Cholinesterase Activity of Serum in Jaundice and Biliary Disease. Proc. Soc. Exper. Biol. & Med. *38*: 363 (1938).
18. Grob, O., Lilienthal, J. L., Jr., Harvey, A. M. & Jones, B. F. The Administration of Di-Isopropyl Fluorophosphate (DFP) to Man. Bull. Johns Hopkins Hosp. *81*: 217 (1947).
19. McArdle, B. Quart. J. Med. 33: 107 (1940).
20. Hicks, C. S. & MacKay, M. E. The Cholinesterase Content of Blood Sera from Normal and Myopathic Subjects. Australian J. Exper. Biol. & M. Sc. *16*: 41 (1938).
21. Vorhaus, L. J., Scudamore, H. H. & Kark, R. M. Measurement of Serum Cholinesterase Activity: A Useful tool in the Study of Diseases of the Liver and Biliary System. Gastroenterology *15*: 304 (1950).
22. Barnes, J. M. & Davies, D. R. Blood Cholinesterase Levels in Workers exposed to Organo-Phosphorous Insecticides. Brit. Med. J. *2*: 816 (1951).
23. Faber, M. Relationship between Serum Cholinesterase and Serum Albumin. Acta. Med. Scandinav. *114*: 72 (1943).
24. Burnett, W. & Cohen, Y. Liver Function after Surgery. Brit. J. Anaesth. 27: 66 (1955).
25. Scurr, C. F. Carbon Dioxide Retention Simulating Curarization. Brit. Med. J. *1*: 564 (1954).
26. Gray, T. C. & Fenton, E. N. S. Carbon Dioxide Retention Simulating Curarization. Brit. Med. J. *1*: 820 (1954).
27. Davis, D. A., Ellis, F. C., Reese, N. O. & Grosskreutz, D. C. The Prolonged Effects of Succinylcholine and Some Possible Explanations for These Phenomena. Anesthesiology *16*: 333 (1955).
28. Gesell, R. & Hansen, E. T. Anticholinesterase Activity of Acid as a Biological Instrument of Nervous Integration. Am. J. Physiol. *144*: 126 (1945).
29. Sawitsky, A., Rowen, M. & Meyer, L. M. A Study of Cholinesterase Activity in the Blood of Patients with Hematological Disease. J. Lab. & Clin. Med. *34*: 178 (1949).
30. Barnard, R. D. A Note on the Depression of Blood Cholinesterase Level following X-ray Therapy and its Bearing on the Mechanism of Radiation Sickness. Med. Rec. *161*: 350 (1948).
31. Butt, H. R., Comfort, M. W., Dry, T. J. & Osterberg, A. E. Values for Acetylcholine Esterase in the Blood Serum of Normal Persons and Patients with Various Diseases. J. Lab. & Clin. Med. 27: 649 (1942).
32. Wright, C. I. & Sabine, J. C. Cholinesterase of Human Erythrocytes and Plasma and their Inhibition by Antimalarial Drugs. J. Pharmacol. & Exper. Therap. *93*: 230 (1948).

33. Torda, C. & Wolff, H. C. Effect of Vitamin K (Menadione) on Cholinesterase Activity, Acetylcholine Synthesis and Striated Muscle. Proc. Soc. Exper. Biol. & Med. *57*: 236 (1944).
34. Pask, E. A. Committee on Deaths associated with Anaesthesia. Anaesthesia *10*: 4 (1955).
35. Glick, D. & Antopol, W. The Inhibition of Choline esterase by Thiamin (Vitamin B.1). J. Pharmacol. & Exper. Therap. *65*: 389 (1939).
36. Roepke, M. H. A Study of Cholinesterase. J. Pharmacol. & Exper. Therap. *59*: 264 (1937).
37. Wright, C. I. & Sabine, J. C. Inactivation of Cholinesterase by Morphine, Dilaudid, Codeine, and Desomorphine. J. Pharmacol. & Exper. Therap. *78*: 375 (1943).
38. Miguel, O. The Effect of Chloroform and Ether on the Activity of Cholinesterase. J. Pharmacol. & Exper. Therap. *88*: 190 (1946).
39. Adriani, J. & Rovenstine, E. A. Anesth. & Analg. *20*: 109 (1941).
40. Davis, J. E. Effects of Certain Anti-Anemic Substances upon Serum Cholinesterase Activity. Proc. Soc. Exper. Biol. & Med. *63*: 287 (1946).
41. Bloch, H. Helvet. chim. acta *25*: 793 (1942).
42. Milhorat, A. T. The Cholinesterase Activity of the Blood Serum in Disease. J. Clin. Investigation *17*: 649 (1938).

NALORPHINE IN THE PREVENTION OF OPIATE-INDUCED NEONATAL NARCOSIS*

FREDERICK PRESCOTT, PH.D., M.R.C.P. (Lond.)**

DEMEROL and, to a lesser extent, morphine, with or without scopolamine, are administered as obstetric analgesics. Relief to the mother is often bought at the cost of respiratory and circulatory depression in the newborn. The extent to which this occurs is variable as it depends on the dose of drug and the time that it is given before delivery. It is more likely to occur if opiates are given to the mother within two or three hours of delivery. The incidence of neonatal asphyxia due to the administration of demerol or morphine to the mother is said to be from 7 to 21 per cent (4, 8, 9, 12, 16). It is not realized that in the adult demerol is almost as potent a respiratory depressant as morphine. If a normal subject breathes a mixture of oxygen with 5 per cent carbon dioxide, respiration is stimulated three- to five-fold. After the administration of demerol this response to carbon dioxide stimulation is reduced to 60 per cent. Either demerol is less depressant than morphine in the newborn or the placenta is less permeable to it, because it causes less depression than morphine in the newborn.

Until recently the treatment of babies born with respiratory and circulatory depression due to over-dosage of the mother with potent analgesics was by mechanical stimulation, artificial respiration, and the administration af analeptics. A specific pharmacological antagonist of morphine is, however, now available in the form of nalorphine or N-allylnormorphine ("Lethidrone" or "Nalline"). This will antagonize most of the pharmacological actions of morphine, such as respiratory and circulatory depression, depression of the reflexes, inhibition of gastro-intestinal movement, increased pressure in the bile duct, and antidiuretic action. Not only is nalorphine a morphine antagonist but it is a pharmacological antagonist to all analgesics with a morphine-like action, such as demerol (pethidine), heroin, levorphan (dromoran), dilaudid, metopon, methadone, and nisentil. It has been used in the resuscitation of patients receiving over-doses of these. In man, approximately 4 to 5 mg. of nalorphine antagonizes 50 mg. demerol, or 5 mg. morphine (1).

In subjects heavily narcotized with opiates, nalorphine dramatically stimulates respiration, restores superficial and deep reflexes, including the cough reflex, and raises lowered blood pressure. The effect is often exerted within a minute or two unless the opiate dosage has been very high.

In heavily morphinized patients nalorphine alters the electroencephalographic pattern from that of deep sleep to that of the waking state (6) and in morphine addicts it evokes the typical abstinence syndrome (15). It probably acts by competing with morphine or other opiates at certain cell receptors and displacing them, just as the sulphonamides compete with PABA, and prevent its being utilized by bacteria. There is an optimum antagonistic dose of nalorphine for a

*Presented at the Annual Meeting of the Canadian Anaesthetists' Society, Toronto, June 20, 1955.

**Wellcome Research Institution, London, England.

given dose of opiate. This means that the dose is critical. If insufficient is given, the opiate is not displaced from the cell receptors; if too much is given, the opiate is displaced and the excess of nalorphine produces its own pharmacological effect. Nalorphine alone has a mild morphine-like action and in 5 mg. to 10 mg. doses in man can depress respiration by 30 to 50 per cent, and produce tiredness, drowsiness, nausea, vomiting, and pallor. In large doses it has an analgesic effect on man (11).

There is some evidence that when nalorphine is given in combination with morphine and in excess of the dose necessary to just antagonize the latter, the effects of the two are additive (10). Lasagna and Beecher (11) state that in man a combination of 5 mg. nalorphine and 15 mg. morphine produces respiratory, depressant, and subjective side effects similar to those obtained with 15 mg. of morphine. Nalorphine is specific only in its antagonism to morphine-like compounds. It is ineffective in relieving respiratory and circulatory depression due to other drugs such as inhalation anesthetics and barbiturates, when administered intravenously or by any other route.

Use in Neonatal Narcosis

Nalorphine was first used by Eckenhoff, Hoffman, and Dripps (6) as an antagonist to neonatal narcosis produced by sedation of the mother with opiates. They gave 10 mg. nalorphine intravenously to mothers ten minutes before delivery. These patients had been given 200 mg. demerol, as well as seconal and scopolamine within the previous five hours. A control group was given saline in place of nalorphine. Babies born under the influence of nalorphine gasped and cried within half the time taken by those whose mothers had not received the drug. Twelve depressed infants received 0.1 to 0.2 mg. nalorphine directly into the umbilical vein within 5 to 10 minutes of delivery. The result in eleven was prompt appearance of respiration, improvement in colour and muscular tone, and sustained crying. In a later study Eckenhoff and his associates (7) described a similar investigation in 1,100 cases of labour. There was a significant reduction in the need for resuscitation, and in the time required for the infants to gasp and breathe when born of mothers who had heavy demerol sedation, and who had also 10 mg. of nalorphine intravenously within 15 minutes of expected delivery.

In 1953 Dr. Paterson and I carried out an investigation on the reduction of neonatal narcosis by nalorphine. The respiration of 203 unselected and consecutive infants whose mothers had been given demerol or "Pantopon" during labour was carefully observed. The total dose of demerol varied from 100 mg. to 300 mg. The doses and times of administration of the drugs were recorded and the foetal heart rate counted every 15 minutes for two hours after giving the drugs. After delivery the cord was not cut until the infant had gasped and cried, and the times when it did this were noted. If the infant did not gasp within 10 seconds of delivery 0.5 mg. nalorphine was given into the umbilical vein. If the infant did not cry within 2 minutes and the cord was still pulsating the dose was repeated. The controls consisted of 205 unselected consecutive obstetric cases, 7 of which were twin births, making the total number of infants 212. Demerol or sometimes "Pantopon" was given to the mother during labour, but the infants were not given nalorphine. The obstetric histories of the nalorphine-treated series and the controls

were similar. Asphyxia was diagnosed in the controls if breathing did not start within 2 minutes, if active resuscitation was necessary, and if the baby was limp and slow to breathe.

In the control series, neonatal asphyxia was present in 34 of 212 infants (16 per cent) and 31 of these required resuscitation. Of the 203 infants in the nalorphine-treated group, 28 (14 per cent) were given nalorphine because of asphyxia, and in 12 of these active resuscitation was required. It was not thought jusifiable to withhold it to see if the infants would eventually breathe spontaneously. It is seen that the incidence of neonatal asphyxia was approximately the same in both nalorphine and control series.

Of the 28 babies that received nalorphine, 8 gasped immediately after the injection and 14 within half a minute. Hence within half a minute, 80 per cent of all treated infants had gasped. Sixteen or 57 per cent cried within 4 minutes after the injection. Of the 21 controls for whom the information was recorded, 8 or 31 per cent cried within 4 minutes. There is a difference between the two percentages, 57 and 31 per cent, but it is not highly significant ($P = 0.19$).

Active resuscitation was needed in 12 of the 28 babies (or 43 per cent) who received nalorphine. In the controls resuscitation was necessary in 31 out of 34, or 91 per cent. The difference between these two percentages is highly significant ($P = 0.001$) in favour of the babies treated with nalorphine.

Discussion

The dosage of nalorphine for adults is probably in the region of 10 mg. The dose for the newborn in this series was 0.5 mg., which was arrived at on the basis that the weight of a newborn infant is about one-twentieth that of an adult. Eckenhoff and his co-workers used 0.1 to 0.2 mg. and Chalmers and Thornberry (3) in a small series employed 0.25 mg. The latter gave this dose to eight infants who had shown no signs of respiration within a short time of delivery and whose mothers had been given morphine or pethidine during labour. The only case in which the treatment was ineffective was attributed to respiratory depression by inhalation anaesthetics. It is possible that a lower dose than the one used in this trial, that is 0.5 mg., would have been effective. Another controlled trial would be necessary to determine this. While no ill effects were attributed to nalorphine in any of these infants, we do know that an overdose in normal adults leads to depression of respiration, sweating, pallor, and depression of the cough reflex. Cappe, Himel and Grossman (2) gave a mixture of 15 mg. morphine, 0.4 mg. hyoscine hydrobromide, and 15 mg. nalorphine to 26 patients in active labour. All the infants except one breathed and cried spontaneously at birth; only one showed respiratory depression. According to these workers the mothers experienced relief from pain. Lasagna and Beecher (11) have shown that while nalorphine has no significant analgesic action in man in doses of 5 mg. or less, in larger doses it is analgesic.

It would seem that the most practical way of giving nalorphine is to administer it to the infant rather than the mother, and only to give it when required. The infant's condition at birth must be carefully assessed, and the cause of asphyxia diagnosed, if possible before any more drugs are administered. Not all cases of neonatal respiratory and circulatory depression are due to excessive dosage of

the mother with opiates. Possibly half are, although Roberts (14) attributes only 14 per cent of cases to over-sedation of the mother. The use of nalorphine should permit the increased use of opiates nearer to the time of delivery than has been considered safe in the past. Hitherto caution has been exercised in giving such drugs within two or three hours of delivery and in repeating the dose even if the mother's condition warrants it. It is also possible that nalorphine will permit the increased use of morphine in obstetrics.

Summary

The use of nalorphine (N-allylnormorphine) as an antagonist to morphine and the opiates is discussed. A dose of 10 mg. in the adult reverses most of the pharmacological actions of clinical doses of the opiates; the dose is critical. Nalorphine can be used to prevent respiratory and circulatory depression in the newborn due to over-dosage of the mother with drugs such as morphine and demerol. If the baby is born with signs of asphyxia, or it does not breathe readily, 0.5 mg. nalorphine is injected into the umbilical vein. Of the babies treated, 80 per cent gasped within half a minute. It is possible that the use of nalorphine will enable opiate drugs to be used nearer the time of delivery.

Résumé

L'auteur traite de l'emploie de la Nalorphine (N-allyl normorphine) comme antagoniste de la morphine et des opiacés. Une dose de 10 mg. chez l'adulte fait disparaître la plupart des effets pharmacologiques des doses cliniques d'opiacés; c'est une dose critique. La Nalorphine peut être employée pour prévenir la dépression respiratoire et circulatoire chez le nouveau-né quand la mère a reçu des quantités nocives de morphine ou de demerol. Si le bébé à sa naissance présente des signes d'asphexie ou ne respire pas immédiatement, on injecte 0.5 mg. de Nalorphine dans le veine ombilicale; 80 pour cent des bébés traités de cette façon commencèrent à respirer en moins d'une demie minute. Il est possible qu'avec l'emploie de la Nalorphine on pourra utiliser des opiacés avant la délivrance.

REFERENCES

1. Bodman, R. I. Proc. Roy. Soc. Med. *46*: 923 (1953).
2. Cappe, B. E., Himel, S. Z. & Grossman, F. Am. J. Obst. & Gynec. *66*: 1231 (1953).
3. Chalmers, J. A. & Thornberry, C. J. J. Obst. & Gynaec. Brit. Emp. *61*: 244 (1954).
4. Cripps, J. A. R., Hall, B. & Haultain, W. F. T. Brit. Med. J. *2*: 498 (1944).
5. Eckenhoff, J. E., Elder, J. D., Jr. & King, B. D. Am. J. M. Sc. *223*: 191 (1952).
6. Eckenhoff, J. E., Hoffman, G. L. & Dripps, R. D. Anesthesiology *13*: 242 (1952).
7. Eckenhoff, J. E., Hoffman, G. L., Jr. & Funderburg, L. W. Am. J. Obst. & Gynec. *65*: 1269 (1953).
8. Gallen, B. & Prescott, F. Lancet *1*: 176 (1944).
9. Gilbert, G. & Dixon, A. B. Am. J. Obst. & Gynec. *45*: 320 (1943).
10. Gruber, C. M. J. Pharmacol. & Exper. Therap. *111*: 409 (1954).
11. Lasagna, L. & Beecher, H. K. J. Pharmacol. & Exper. Therap. *112*: 356 (1954).
12. O'Reilly, P. J. Lancet *2*: 1012 (1948).
13. Paterson, S. & Prescott, F. Lancet *1*: 490 (1954).
14. Roberts, H. Brit. Med. J. *2*: 590 (1948).
15. Wikler, A., Fraser, H. F. & Isbell, H. J. Pharmacol. & Exper. Therap. *109*: 8 (1953).
16. Winters, H. S., Garcia, C. R. & Lubin, S. Am. J. Obst. & Gynec. *61*: 629 (1951).

ARTIFICIAL HIBERNATION: A REPORT OF FORTY-TWO CLINICAL CASES*

GÉRARD MIGNAULT, M.D.**

ON SEVERAL OCCASIONS the subject of Artificial Hibernation has been discussed before the Canadian Anaesthetists' Society by Dr. Fernando Hudon of Quebec City. We thought, therefore, it would be of some interest to present a series of 42 clinical cases of which 22 were medical and 20 were surgical.

From the concepts of Claude Bernard, Cannon, Reilly and Selye, Laborit evolved his technique of "Artificial Hibernation," by which he transforms a homeothermic organism to a poikilothermic organism.

Summarizing these two concepts, we can say that a homeothermic being is one who can maintain a constant internal environment in spite of a changing external environment. Under conditions of severe stress the homeothermic state becomes a disadvantage because the expenditure of energy in maintaining this constancy will tend to exhaust the organism and to hasten death. When an organism approaches the poikilothermic state, the constancy of the internal environment is partly sacrificed, energy is conserved, and life is prolonged.

Laborit concluded that artificial hibernation, utilizing the "lytic cocktail," could be a valuable means of maintaining life of patients *in extremis*.

Our modest series of cases would seem to bear this out. There were patients whose lives were prolonged for periods as long as two months.

The series was divided into two groups: first, the surgical, where hibernation was used only for the period of surgery; and second, the medical, where this technique was employed as a resuscitative measure. Some of the patients of the second group went on to further treatment by surgery during the period of hibernation.

MEDICAL CASES (Table I)

In our series of medical cases, 14 out of 22 patients were *in extremis*; every conventional treatment had failed, and death was imminent.

Six out of these fourteen patients represented cases of cerebro-vascular accidents associated with hyperthermia. All of them showed clinical improvement during hibernation. Four died upon emerging from hibernation; the other two died two months later. Post-mortem examinations demonstrated lesions incompatible with life in every case.

Another five of these fourteen patients had severe head injuries and they were also *in extremis* when they were submitted to hibernation. All were operated on either before or during hibernation. Four out of the five did well and had complete recovery. The hibernation lasted from three to ten days depending upon the reaction of the patient to attempts at rewarming. The patient who died was a 68-year-old arterio-sclerotic male, who had quite extensive and profuse subdural bleeding. This was on the fourth day of hibernation following an exploratory craniotomy.

*Presented at the Annual Meeting of the Canadian Anaesthetists' Society, Toronto, June 21, 1955.

**Hôtel-Dieu Hospital, Montreal.

TABLE I

MEDICAL CASES SUBMITTED TO ARTIFICIAL HIBERNATION

Central hyperthermia following	Cerebro-vascular accidents	6 cases
	Severe cerebral trauma	5 cases
	Surgery of the posterior fossa	2 cases
	Fat embolism	1 case
Postoperative shock with lower nephron nephrosis		1 case
Postoperative thyroid crisis		1 case
Mitigated hibernation for psychoneurosis		3 cases
	recurring infection	1 case
Postoperative sedation in drug addiction		2 cases
		22 cases

Two other cases, of central sustained hyperthermia following surgery of the posterior fossa, were helped by mitigated hibernation. The temperature was lowered and they recovered.

One of the cases was a severe postoperative shock with lower nephron nephrosis. In my opinion, this patient was aided by hibernation: diuresis followed, the blood pressure stabilized, and correction of the electrolyte balance was made possible. However, the patient had severe pulmonary atelectasis which resisted treatment and at the first attempt at rewarming she died following a tracheobronchial toilet.

Another case was that of a man who did not adhere to the therapy for his hyperthyroidism. Following emergency surgery for a kidney abscess, a thyroid crisis occurred which was promptly controlled by hibernation.

Another four patients had modified hibernation. Three of those were treated by induced sleep of seven to ten days' duration for psychoneurosis. There was doubtful temporary improvement of the condition. The fourth case was that of a young woman with abscesses recurring over a period of two years. She was cured of her infection by hibernation. She was found to be a case of drug addiction with self-mutilation and is still doing well four months after treatment.

SURGICAL CASES (Table II)

We believe that surgery can derive benefit from the hibernation technique in two ways. First, it can be extended to newer and wider fields, for example, to brain surgery involving interruption of the circulation or to cardiotomy for repair of congenital defects (we have had no experience with this type of case[1]). Secondly, patients in poor physical condition subjected to long and extensive surgery, will be helped by the technique. Our series of 20 cases belong to this group.

There were 6 cases of radical neck dissection with simultaneous wide excision of the primary cancerous tumours; 3 cases in which extensive blood loss was anticipated; 3 cases of toxic goiter; and 8 other cases where patients in poor physical state were submitted to extensive surgery.

[1]Since the presentation of this paper, we have had a case of an aneurysm of the anterior communicante; the patient underwent surgery under artificial hibernation, the rectal temperature being lowered to 83°F. Ligation and resection of the aneurysm were possible and the patient is doing well five months after operation.

TABLE II

SURGICAL CASES SUBMITTED TO ARTIFICIAL HIBERNATION

Radical neck dissection with excision in continuity of the cancerous lesion	6 cases
Massive haemorrhage during surgery	3 cases
Toxic goiter	3 cases
Very poor risk patients	8 cases
	20 cases

Hibernation helps in these cases by reduction of the homeothermic response to surgical and haemorrhagic stresses, and by potentiation of anaesthetic agents. Weaker and less toxic drugs can be used. Nitrous oxide with higher concentrations of oxygen supplemented with small amounts of demerol is all that is necessary in most cases. Such a technique disturbs these patients very little, yet they are well protected against pain and harmful reflexes. Minimal hypothermia reduces even further their metabolic requirements. In this state of "reduced life," not only do they tolerate extensive surgery well, but they have much less postoperative distress and yet are co-operative.

The most interesting cases in our series were those of radical neck dissection. Prior to the use of the hibernation technique, the maintenance of blood pressure during surgery in this type of case, was always a problem even though more blood was replaced than the estimated loss. This was particularly true for the aged patients (we had three over 70 and one over 90), who, having been subjected to the stress of extensive and prolonged gland dissection, were then exposed to additional haemorrhagic stress from the wide excision of the primary growth. Not only has artificial hibernation minimized the dangers of such extensive surgery but it has also markedly reduced postoperative morbidity, especially following pulmonary complications. As a matter of fact, these patients responded to the spoken voice as soon as they were extubated, and there was an absence of nausea and vomiting with early retention of fluids. A few were ambulatory the day of the operation. Minimal sedation was required, and in some instances, no opiates at all were given.

The course in the three toxic goiter cases was uneventful except for a transient tachycardia.

In the three haemorrhagic cases, the patients did unexpectedly well.

The seven patients who were poor surgical risks did strikingly well, except one. This was a case of an oesophagectomy on a 73-year-old malnourished patient. He died during the third postoperative day. The post-mortem examination showed bleeding from the operative site. This was the only death of the surgical series.

SUMMARY AND CONCLUSION

Our observations of a series of 42 patients subjected to Artificial Hibernation have been presented with emphasis on the resuscitative value of this technique. Artificial hibernation is a delicate and exacting technique which has widened the scope of surgery and of resuscitation.*

*I should like to thank Dr. Harry Slater and Dr. Sheridan for their kind help with the translation of the paper.

Résumé

Une étude clinique sur 42 cas d'hibernation artificielle est présentée dont 22 cas médicaux et 20 cas chirurgicaux.

Cette étude, à notre avis, démontre bien l'extension possible de la réanimation grâce à l'hibernothérapie. Cette technique est également d'un grand secours en chirurgie chez les grands malades.

REFERENCES

1. Laborit, H. Réaction organique à l'agression et choc. Masson & Cie (1952).
2. Laborit, H. & Huguenard, P. Pratique de l'hibernothérapie en chirurgie et en médecine. Masson & Cie (1954).
3. Laborit, H. Résistance et soumission en physio-biologie: "L'Hibernation Artificielle." Masson & Cie (1954).
4. Smith, A. & Fairer, J. G. Hibernation Anaesthesia in Major Surgery. Brit. Med. J., Dec. 5: 1247 (1953).
5. Dundee, J. W., Scott, W. E. B. & Mesham, P. R. The Production of Hypothermia. Brit. Med. J., Dec. 5: 1244 (1953).

PREPARATION OF THE PATIENT FOR INTRATHORACIC SURGERY*

JEAN-PAUL DECHÊNE, M.D.**

As you know, opening of the thorax, whether it involves an attack upon the lungs, heart, great vessels, or oesophagus, imposes special problems in the care of the patient if the anaesthetist is to ensure his safe conduct through the preoperative period.

LUNG SURGERY

Preoperative Evaluation

Except for those with acute traumatic emergencies the majority of patients with pulmonary diseases requiring surgery can be assessed preoperatively and optimally prepared for treatment. A careful history of the disease, a good physical examination, and the following specialized examinations are considered very useful in the preoperative evaluation of the patient.

A. *History of the patient*

Previous anaesthesia and drug allergy, anaemia, defects in blood coagulation, weight loss, avitaminosis, metabolic deficiencies, and psychic preparation are to be considered. Cough habits, quantity and character of sputum, extent and duration of smoking habits, and oro-dental hygiene should be evaluated.

B. *Physical examination*

Much valuable information can still be obtained by listening to the chest: rales, ronchi, character of breathing, tracheo-bronchial secretions can be best evaluated by physical examination.

C. *Specialized examinations*

The necessity and advantages of a preoperative X-ray of the chest are self-evident. Often laminography and bronchography must be included. Complete evaluation of pulmonary function and cardiac reserve is imperative. Laboratory examinations should also be made.

Pulmonary function studies may be divided into the mechanical and alveolor respiratory phases. Mechanical tests consider the lungs as bellows and the tests are either static in type (for vital capacity, inspiratory capacity, tidal air, expiratory reserve, residual capacity, total lung volume) or dynamic (for timed vital capacity, valking ventilation and maximum breathing capacity); sometimes bronchospirometry is necessary. Alveolar respiratory tests are concerned with the quantity and quality of gaseous exchange at the inspiratory, alveolar, capillary, and tissue levels. They include tests for intra-pulmonary gas mixing, diffusion tests, and arterial blood studies.

For the evaluation of *cardiac reserves*, the venous pressure and circulation time are two very helpful tests. Moot's test is an additional good criterion of cardiac reserves. This test multiplies the pulse pressure by 100 and the figure obtained is

*From a Panel Discussion on "Anaesthesia and the Open Chest," held, under the direction of Dr. S. M. Campbell, at the Annual Meeting of the Canadian Anaesthetists' Society in the Banting Institute of the University of Toronto, June 20, 21, and 22, 1955.

**Hôpital Laval, Ste-Foy, Québec.

divided by the diastolic pressure. Electrocardiogram tracings are taken before and after exercises.

The following *laboratory examinations* are also done before anaesthesia for lung surgery: urinalysis; complete blood count; hematocrit reading; blood volume; total blood protein; blood typing and Rh factor; pre-transfusion cross-matching; bleeding and coagulation time; prothrombin time (quick method); sed rate; phenol-sulfonephtalein test; blood urea; sputum culture; antibiotic sensitivity.

Preoperative Care

From the clinical findings, the clinical examination, and the specialized examinations (X-ray studies, cardio-pulmonary function tests, and laboratory tests) the anaesthetist may arrange a better preparation for the patient scheduled for lung surgery.

A. *Hygiene*

Smoking should be reduced. Tracheo-bronchial irritation should be avoided. Orodental hygiene should be improved. Upper respiratory and sinus infections should be controlled. Alcoholism should be under control.

B. *Blood, electrolyte, and metabolic deficiencies*

Anaemia, blood volume, fluid balance, avitaminosis, and metabolic deficiencies should be effectively controlled with iron, transfusions, electrolyte solutions, vitamins, and a good diet. Even though the patient is receiving a well-balanced full diet, it should be supplemented by Thiamin (40 mg./day), nicotinic acid (300 mg./day), Riboflavin (40 mg./day) and ascorbic acid (50 mg./day). Patients who have a tendency to bleed should also receive vitamin K (75 mg./day).

C. *Antibiotic therapy, INH problems*

Tuberculous patients require specific antibiotic therapy: streptomycin, Dihydrostreptomycin, P.A.S., and I.N.H. Patients under treatment with isonicotinic acid derivatives, especially the isopropyl derivative, have shown oxygenation problems and convulsions at the anaesthetic period. To avoid this complication we now routinely stop this medication two to three weeks before surgery.

D. *Aerosol therapy and drainage*

If needed, aerosol therapy with penicillin or streptomycin may be instituted before surgery. Postural drainage remains an important adjunct to all preoperative preparation.

E. *Pulmonary insufficiency*

Pulmonary insufficiency is treated by respiratory exercises under the supervision of a trained physiotherapist. Patients are taught how to breath and cough. Emphysematous patients are given positive pressure, ACTH treatment, and also Aminophyllin which is mainly helpful when there is an elevation of the venous pressure. Bronchodilators such as "Vaponefrin" given in aerosol may be indicated in obstructive endo-bronchial lesions.

F. *Premedication*

For premedication, less depressive sedatives are used routinely. "Demerol" ("Pethidine") associated with Atropine seems to be in favour. A few use only

barbiturate with Atropine. Especially for nervous and anxious patients, a few others use Phenothiazine derivatives: Promethazine, Phenergan, Chlorpromazine (Largactil), associated or not with barbiturates during the immediate preoperative days.

G. *Cardiac failure*

Cardiac failure remains one of the prime causes of difficulty in the postoperative period and is the most common cause of mortality in the early postoperative period. Therefore digitalization of the patient has been used preoperatively if the history or physical examination suggest cardiac embarrassment.

Heart and Great Vessels Surgery

Preoperative Evaluation

The preoperative selection of all patients must be made by the anaesthetist in collaboration with the cardiac surgeon and cardiologist. The compiling of the history and the evaluation of the severity of symptoms in relation to the physical findings and specialized examinations enable the anaesthetist to forecast whether it will be possible to maintain adequate heart action during the epicardiac and intracardiac manipulations.

A. *History of the patient*

The patient is evaluated by a careful history of the disease and general condition (history of heart failure, history of systemic embolism, total body weight, diuresis, insomnia and nervousness), and by repeated observations of heart rate, respiratory rate, blood pressure, and metabolic deficiencies.

B. *Physical examinations and specialized examinations*

Important too are physical examinations of the heart and specialized examinations such as: X-ray studies, electrocardiogram tracings, pulmonary function tests, venous pressure and circulation time, angio-cardiography, and cardiac catheterization. The same laboratory examinations suggested for lung surgery are also very useful for the right evaluation of the cardiac patient.

C. *Hypotension and Keown's test*

As Kenneth K. Keown says in his chapter on "Anaesthesia for Cardiac Surgical Operations": "Hypotension is extremely common in all patients with acquired lesions of the heart except those with aortic insufficiency or coronary artery disease, and a very practical phase of preoperative evaluation and anaesthetic management is the determination of the systolic and diastolic blood pressure of the candidate for heart surgery in the supine position, in comparison with that obtained with the patient in the lateral position, which will usually be used during surgery. This is done prior to any preliminary medication, in an effort to determine the normal for the specific individual. In general there is a decrease in systolic pressure of 10 mm. of mercury and a slowing of the heart rate." This lowering of the blood pressure, according to Kenneth Keown, is the base line for premedication.

Aside from the circulation itself, it is wise to test the response of the patient to the planned premedication.

For this purpose, preoperative drugs (Barbiturate, Demerol, Atropine) are

given and the patient's response is noted for the following hours with respect to his pulse, blood pressure, breathing, and any other reactions.

Some doctors also routinely evaluate the adrenal cortical capacity by the eosinophil depression test and use this to decide whether adrenal cortical support will be necessary during and after operation.

Preoperative Care

The cardiac patient is prepared for surgery by minimizing decompensation, to give the patient the greatest possible cardiac reserve. This is done by the usual methods of correcting cardiac failure such as bed rest, oxygenotherapy, digitalis, correcting the electrolyte balance, diuretics, low-salt diet, liver damage improvement and antibiotics; in addition, if indicated, anticoagulants and proper sedation.

A. *Hygiene*

Before cardiac surgery as before lung surgery, smoking should be reduced, orodental hygiene improved, upper respiratory infections and metabolic deficiencies controlled, and a good diet supplemented with vitamins should be instituted.

B. *Digitalis*

The goal in the immediate preoperative period is to bring the patient into the best possible state of cardiac compensation. Digitalis is used for congestive heart failure or atrial fibrillation.

The proper regulation of digitalis is important. Over-dosage is manifested by ventricular conduction or alterations in the pace maker. It is important to avoid dangerous arrythmia at the time of operation. Administration of potassium (3.0 gr./day) may be useful since hypokalaemia potentiates the toxic effects of digitalis. However, this supplemented potassium must be withheld the day before operation so that the patient does not face the usual postoperative oliguria with an excess of potassium. It is usually best to maintain the form of digitalis that the patient has been receiving. The dose is regulated so that the apical rate is consistently in the range of 80–90 per minute.

C. *Quinidine and Procaine Amide*

The routine prophylactic use of Quinidine or Procaine (either the amide or the hydrochloride) before or during operation is contra-indicated because of the obvious undesirability of depressing the myocardium. Hearts depressed by such drugs go into a state of arrest more frequently.

D. *Electrolyte balance*

The authors found that generally stores of sodium in the body and in serum were in the normal range but total body water was almost invariably increased.

A few patients, generally those who have had severe congestive heart failure requiring prolonged sodium restriction and vigorous mercurial diuresis, manifest an actual depletion of sodium stores because of restriction and diuretics. The desperately ill patients have a low serum sodium value. A value in the range of 118 to 125 milli equivalents is considered by Black and Harken as a sign of impending death (in a week). The management of this electrolyte problem consists of continued salt restriction and limitation of fluid to 1000 to 1500 cc. a day to avoid serum dilution; daily weighing of the patient is a most important step. The

urinary sodium concentration should also be measured. Moore says: "Salt loss through the kidneys may exist. In this situation, urinary sodium is elevated to more than 30 milli equivalents per litre. Below 25 milli equivalents in urine with a low serum sodium the renal tubules are considered normal. In general it is better to delay operation until the serum sodium level reaches 130 milli equivalents per litre or above."

E. *Diuretics*

In the preparation of the cardiac patient for operation the judicious use of diuresis is of the utmost importance. The studies of Wilson and his associates have repeatedly demonstrated a high total body water even in the absence of gross oedema; furthermore, the diuretic response of many non-oedematous cardiac patients justifies this step. Because the diuresis often leaves the patient fatigued on the following day, the diuretic should be given at least forty-eight hours before operation. Even patients with no obvious oedema are given a dose of 1 cc. of Mercuhydrin early in the preoperative period. If the patient has a marked response to the first dose of the mercurial diuretic it should be repeated at intervals of forty-eight to seventy-two hours until the "optimal dry weight" has been reached. Several conditions may explain a lack of response to 1 cc. of Mercuhydrin: the patient may be in a satisfactory state of compensation and not have occult oedema; the serum chlorides may be low, necessitating ammonium chloride in doses of 6 to 8 gm. a day for several days before the mercurial diuretic is repeated; or a 2 cc. dose may be indicated.

Potentiation of diuretics may also be obtained by the administration of aminophylline (0.25 to 0.5 gm.) by vein half an hour after the mercurial diuretic.

F. *Low-salt diet*

Most patients who have had evidence of congestive heart failure will have been placed on a low-salt diet (200 mg. of sodium) at some time before hospital admission, but if this has not been done, the diet obviously should be instituted as an adjunct to the measures discussed above for the preoperative period, with the sole exception previously mentioned.

G. *Liver damage*

With patients who have definite enlargement of the liver, operation has been delayed for at least a week or ten days for rest and preparation. The liver profile of bilirubin, total protein and albumin-globulin ratio, prothrombin time and thymol turbidity is obtained to document the clinical impression of a liver disturbance. These patients are placed on a high-carbohydrate, low-fat diet, with vitamin B supplements in addition to choline, methionine, inositol, and folic acid.

Obviously, a patient who has been on long-term Dicumarol therapy for arterial embolism should be taken off the drug and the prothrombin time allowed to return to normal before any operative procedure is contemplated. Vitamin K is administered for any abnormally prolonged prothrombin time not traceable to anticoagulant therapy.

H. *Antibiotics*

Forty-eight hours before operation parenteral injection of penicillin is begun. This is supplemented by aerosol penicillin and streptomycin in patients with mitral stenosis in whom chronic pulmonary suppuration is present.

J. *Hematocrit*

In congenital heart disease with increased hematocrit, dehydration must be avoided before operation because of the danger of cerebral thrombosis.

K. *Proper sedation*

The pre-anaesthetic medication is directed towards reducing physical and mental strain and lessening cardiac irritability. According to Keown, for mitral stenosis Pentobarbital sodium ("Nembutal") 0.10 to 0.20 gm. (gr. 1½–gr. 3) is given by mouth the night before operation. Secobarbital sodium 100 mgm. is ordered if the systolic blood pressure in the right lateral position is 100 mm. of mercury or higher by palpation of the left radial artery. If the pressure is between 90 and 100, 50 mgm. of Secobarbital is ordered. If the pressure is less than 90, no barbiturate is given. This is given by mouth 60 minutes prior to induction of anaesthesia. Atropine Sulphate is ordered for hypodermic administration at the same time, the dose being determined by the radial pulse rate. If the pulse rate is 60/min. or less, Atropine 1/100 is given; for a pulse rate between 60 and 80, gr. 1/150 Atropine; from 80 to 100, gr. 1/200 Atropine. In aortic stenosis, Glyceryl Trinitate, 0.3 (gr. 1/100) to 0.6 mg. (gr. 1/200), is added to the same pre-medication as for mitral stenosis for prevention or treatment of angin-episodes. For tricuspid stenosis, preliminary medication is similar to that given to patients with aortic or mitral stenosis. For mitral insufficiency, the medication is about the same and we must remember, always according to Keown, that these cases are the most serious and the more difficult to manage: if in the lateral position the systolic pressure is less than 80 mm. of mercury, the patient should be turned back to supine position and the operation cancelled for that day. For aortic insufficiency and coronary artery diseases a barbiturate followed by Demerol and Atropine is given. Glyceryl trinitate is also given in coronary disease. According to McQuiston, for congenital heart lesions, a 2- or 3-month-old infant, weighing only 7 or 8 pounds, is given Morphine Sulphate 1/48 and Atropine Sulphate 1/300; as the age increases the amount of Morphine Sulphate and Atropine Sulphate is increased so that a 4-year-old child receives Morphine Sulphate gr. 1/8 and Atropine Sulphate gr. 1/200. For children 5 years of age to puberty, Morphine Sulphate gr. 1/8 and Scopolamine gr. 1/200 is usually administered. Age and not weight is the determining factor of the size of the dose. With congenital heart lesions, some are using 1 mg. of Demerol or of Meperidine per pound of body weight in children up to puberty or those weighing 100 pounds.

Oesophagus Surgery

Preoperative Evaluation and Care

Patients requiring oesophagectomy present profound disturbances in fluid and nutritional balance; and we know that nutritionally depleted patients are relatively poor anaesthetic risks. Before operation, a partial restoration of body stores and satisfactory restoration of the fluid balance performed by the anaesthetist in co-operation with the surgeon, will permit for these patients the safe performance of the transthoracic resection of the oesophagus.

Oesophagectomy

To realize this for oesophageal operations, the anaesthetist requires the routine preoperative laboratory examinations as for other surgery. The anaesthetist must

study with the surgeon the history of the patient and decide whether or not the patient is able to support the resection and if so, when the patient will be ready for surgery. A careful investigation of the cardio-respiratory system is imperative before performing surgery.

Patients who have had congestive heart failure, coronary artery disease, or auricular fibrillation or flutter are prepared cautiously when the intravenous route is used for alimentation. Orodental hygiene should be attended to and antibiotics given. In preparing such a patient for surgery, an oesophageal lavage must be done and a gastric tube passed if possible into the stomach prior to the patient's being taken to the operating room. Proper premedication must also be ordered by the anaesthetist.

Oesophageal Repair

A patient needing this treatment may be only a few days old and very frequently a tracheo-oesophageal fistula exists. An aspiration pneumonia may be present. To reduce the incidence and severity of aspiration pneumonitis, the infant is wrapped in blankets, placed in an oxygen tent with the foot of the bed elevated slightly, and turned hourly from the prone position to the right and then to the left side.

Oesophagus

In order to reduce the danger of aspiration of mucus and saliva from the blind upper oesophageal segment, a small soft rubber catheter is passed into this pouch via the nose. Gentle suction is applied at frequent intervals.

Nutritional depletion is usually not a significant factor in newborn infants with congenital atresia, when the diagnosis is made within the first day or two after birth. The problem of dehydration is more important at this time. Fluids may be administered by hypodermoclysis or intravenously.

The infant is given gr. 1/500 of Atropine Sulphate intramuscularly about ten minutes before being transported to the operating room.

Résumé

Au cours de ce travail, nous allons démontrer le rôle joué par l'Anesthésiste dans la préparation du patient pour chirurgie thoracique.

Anesthésie et chirurgie pulmonaire

A. Une histoire détaillée de la maladie, un examen physique complet et certains examens spéciaux tels les radiographies, les tests de la fonction cardio-respiratoire, et les examens routiniers de laboratoire sont considérés comme très utiles pour l'évaluation d'un risque chirurgical. Cette évaluation doit se faire de concert avec l'Interniste et le Chirurgien.

B. Suivant les renseignements que lui ont fournis ces examens, l'Anesthésiste doit: (*a*) Si nécessaire, instituer le traitement hygiéno-diététique le plus approprié à son patient; (*b*) Restaurer les déficiences métaboliques, l'équilibre électrolytique, et surtout le volume sanguin; (*c*) Installer de l'aérosolthérapie si nécessaire; (*d*) Diriger le physiothérapeute et faire faire du drainage postural s'il y a lieu; (*e*) Améliorer si possible l'insuffisance respiratoire; (*f*) Cesser, si le malade en reçoit, l'Isoniazide et surtout l'Iproniazide afin d'éviter en cours

d'anesthésie, certains troubles de l'hématose et certaines complications neurologiques d'ordre convulsif; (*g*) Décider de la technique anesthésique à employer; (*h*) La veille de l'intervention, ordonner la prémédication la moins dépressive possible (on conseille surtout le "Demerol" associé à "l'Atropine" et chez les anxieux, le "Phénergan" ou le "Largactil."

Anesthésie et chirurgie cardiaque et des gros vaisseaux

Ici encore, une histoire détaillée de la maladie, un examen physique complet et certains examens spéciaux (électrocardiographie, angio-cardiographie et cathétérisme cardiaque) sont considérés comme très utiles pour l'évaluation d'un risque chirurgical. Egalement, cette évaluation doit se faire de concert avec le cardiologiste et le chirurgien.

Le test d'hypotension de Keown a certainement une grande importance et certaines gens recommandent en outre d'étudier la réponse du patient à la prémédication future.

L'opéré cardiaque est préparé en minimisant la décompensation et en augmentant le plus possible ses réserves cardiaques.

Ceci est fait par le repos au lit, l'oxygénothérapie, la digitalisation, la balance des électrolytes, les diurétiques, la diète hypo-salée, l'amélioration de la fonction hépatique et s'il y a lieu, les anticoagulants, les antibiotiques et une sédation appropriée.

Pour la prémédication, la ligne de conduite de Keown semble être la plus suivie.

Anesthésie et chirurgie de l'oesophage

A. Les patients nécessitant une résection de l'oesophage présentent la plupart du temps, des troubles sérieux de la nutrition. Aussi, c'est un devoir impérieux pour l'Anesthésiste de corriger ces troubles avant de permettre l'intervention.

Si la voie I.V. doit être employée et si ces patients montrent certains signes de défaillance cardiaque, on doit le faire avec précaution. Encore là, la fonction cardio-respiratoire doit être bien étudiée avant l'intervention afin de déterminer si le patient peut la supporter.

Une sonde gastrique doit toujours être présente et le lavage de l'estomac doit être fait avant de diriger le patient à la salle d'opération.

B. Lorsqu'une fistule trachéo-oesophagienne existe, afin de réduire l'incidence de la pneumonie d'aspiration, l'enfant, en l'occurrence le nouveau-né, est enveloppé dans ses couvertures, placé dans la tente d'oxygène avec le pied du lit élevé et tourné aux heures, de la position ventrale à la position latérale tantôt gauche, tantôt droite. Une sonde gastrique doit être mise en place et la déshydratation corrigée adéquatement.

Une fois l'enfant bien préparé, il est dirigé vers la salle d'opération et de "l'Atropine" à la dose de gr. 1/500 est administré environ 10 minutes avant l'intervention.

En conclusion, nous pouvons dire que les succès actuels de la "Chirurgie Thoracique" sont, dans une grande mesure, dus à la bonne préparation des patients et nous espérons avoir démontré le rôle joué par l'Anesthésiste dans cette préparation.

PHYSIOLOGICAL DISTURBANCES DUE TO OPENING AND OPERATING WITHIN THE CHEST*

WILLIAM G. CULLEN, M.D.**

TODAY, intrapleural thoracic surgery consists of three main types: (1) surgery of the lungs; (2) surgery of the heart and the great vessels; (3) surgery of the upper gastrointestinal tract via the transthoracic approach.

As the main organs of the thorax are the heart and lungs and their associated blood vessels, let us consider briefly their function in the *closed* chest before attempting to determine how this physiology is disturbed by *opening* and *operating* within the chest.

Since the heart and lungs function as a unit, it is difficult to consider them independently. The main function of this cardiopulmonary unit is to furnish a continuous supply of oxygen and nourishment to all cells of the body and to remove the carbon dioxide and metabolic end products. Thus an accurate knowledge of the partial pressure of both oxygen (arterial p O_2) and carbon dioxide (arterial p CO_2) in the arterial blood is essential to determine the cardiopulmonary function (1).

Normal values for arterial p O_2 range from 71.5 to 100.1 mm Hg.

Values below 70 mm Hg are pathological.

This evidence of oxygenation is much more valuable than an evaluation of the oxygen saturation of the haemoglobin.

Normal values for arterial p CO_2 =

$$35.0 \pm 1.44 \text{ mm Hg.}$$

or

$$46.8 \pm 0.73 \text{ volumes per cent}$$

To obtain efficient gas exchange in the lungs the following four main factors must be adequate:

I. *Ventilation*, designated as V; or more specifically alveolar ventilation
II. *Distribution*, i.e., gas mixing in the lungs
III. *Diffusion*
IV. *Circulation*

Alveolar ventilation (V) is not only the first and most important single factor, but is the variable that is most readily influenced by the anaesthetist and the surgeon.

FIVE CONCEPTS IN CARDIOPULMONARY PHYSIOLOGY (2)

1. The lungs are said to be passive structures in so far as air movement is concerned. Under natural conditions air movement is entirely a result of and directly proportional to the changes in the volume of the thorax caused by movement of

*From a Panel Discussion on "Anaesthesia and the Open Chest," held, under the direction of Dr. S. M. Campbell, at the Annual Meeting of the Canadian Anaesthetists' Society in the Banting Institute of the University of Toronto, June 20, 21, and 22, 1955.

**Department of Anaesthesia, Queen Elizabeth Hospital and McGill University, Montreal.

the ribs and diaphragm. On the other hand, Lucas (3) has drawn our attention more particularly to the dynamics of the bronchial tree, suggesting that the latter is not a passive structure but one which expands and elongates during inspiration and shortens during expiration. The wall of the whole bronchial tree, with the exception of the alveoli, contains an intricate pattern of smooth muscle and elastic tissue. Ciliary action has been described well and stressed rightly by Negus (4, 5) but few anaesthetists give its significance any thought. Tremble (6) has beautifully illustrated with moving pictures "the waving fields of grain" covered by "a blanket of mucus" (4).

Although anaesthetists have a time-honoured maxim "Keep the Airway Clear," their attention is too often concentrated on the *upper* respiratory tract, and a *lower* respiratory obstruction is neglected.

Nosworthy (7) has again reminded us that "it is upon the patency of the bronchiolar lumen and the quiescence of the bronchial reflexes that smooth anaesthesia largely depends." This site is of particular significance as we emphasize the importance of alveolar ventilation.

Incidentally, asthma is considered (8) to be a derangement caused by uneven ventilation of the lungs. The narrowing of the bronchial lumen may vary greatly in different parts of the lung but the major cause of occlusion is viscid secretions rather than spasm of bronchial muscle.

Herxheimer (9) has given attention to the activity and the level of the diaphragm. Emphysema, even in milder degree, is associated with a low but active diaphragm, whereas the obese patient with a large amount of abdominal fat has a relatively high diaphragm that moves poorly.

Another factor influencing the respiratory apparatus is the so-called compliance of the lung, i.e., the inherent ability to distend and collapse.

In addition, the lungs are capable of considerable over-distension before showing signs of impaired function. However, over-distension is a relative matter, for the simple change from the recumbent to the erect position in a normal person actually doubles the size of the lungs; i.e., there is 100 per cent over-distension (10).

2. The lungs and thorax act as the "pump" which brings air to the pulmonary capillary bed for gaseous exchange. Normally there is a tremendous pulmonary reserve, whereas cardiac output can only be increased four or five times.

3. The lung *per se* is an enormous capillary bed, suspended in air, which can transmit a widely variable volume of blood with relatively slight changes in pulmonary artery pressure (2). As the vascular resistance is low, the pulmonary circulation time is extremely short. It will only take about four seconds for blood from the right ventricle to reach the left auricle via the pulmonary system (1).

4. The body is possessed of an adaptive mechanism whereby circulation is shunted from a collapsed or diseased area to a more normal area. Poorly or unventilated but still distended portions of lung have a diminished pulmonary capillary blood flow.

5. The remarkable degree to which the pulmonary capillary bed can be enlarged by increase of cross-section area of the capillaries and perhaps by opening of previously nonperfused capillaries is demonstrated by the fact that, when both

lungs are approximately normal, ligation of a pulmonary artery to one lung causes only transitory elevation of the pulmonary artery pressure (2).

Physiological Disturbances

Whereas our knowledge of human cardiopulmonary physiology with the closed chest is developing and changing very considerably, actual studies during thoracic surgery with the open pneumothorax are few. Fourteen years ago, Nosworthy (11) clearly depicted in a classical manner, with linear drawings, the problems arising when the chest is opened. Later Crafoord (12), Organe (13) and others also described this complex situation.

When a patient, with pathology in the thorax, is anaesthetized, placed in some specific position, and then has the left or right side of his chest *opened widely* for some intrathoracic surgical procedure, various physiological disturbances may appear. It is therefore a specific challenge to the anaesthetist and the surgeon to foresee and prevent all such disturbances.

Efficient alveolar ventilation, in the fullest sense of the phrase, should be the watchword of every anaesthetist and if it were constantly heeded, almost all of the following undesirable disturbances could be prevented:

Physiological Disturbances

I. Disturbances of Respiratory Dynamics
   1. Lung collapse and shift of the mediastinum
   2. Paradoxical respiration
   3. Mediastinal flap or flutter
II. Disturbances due to Lack of Oxygen
III. Disturbances due to Excess Carbon Dioxide
IV. Disturbances of Cardio-Circulatory Dynamics
   1. Cardiac output
   2. Cardiac arrhythmias
   3. Cardiac arrest
V. Disturbances due to Posture
VI. Disturbances due to Reflexes
VII. Disturbances due to Loss of Body Heat

I. *Disturbances of Respiratory Dynamics* (14)

1. *Lung collapse* and *shift of the mediastinum*

When the pleural cavity is widely opened the previous negative pressure is converted into that of the surrounding atmosphere. The pulmonary elastic tissue tends to collapse the exposed lung. Also the mediastinum moves towards the opposite side, tending to compress the other lung. This latter effect is more marked in the lateral than in the prone position (15). The situation may be aggravated by gravity causing some overload in the pulmonary vascular bed of the lower lung.

Bronchospirometry studies with the patient in the lateral position and the chest closed show that the lower lung has the greater respiratory exchange. However, when the upper side of the chest is open, the tidal volume to the lower

lung is reduced resulting in inadequate ventilation (15). Spontaneous respiration with the open chest is far too turbulent for cardiac surgery and the associated hypoxia and reflex shock from mediastinal flap would be fatal in many of these poor-risk cases (16).

2. *Paradoxical respiration*

This to-and-fro movement of air from one lung to the other makes the movements of the lung on the open side paradoxical, since it collapses with inspiration and expands with expiration.

During such procedures as thoracoplasty, paradoxical respiration may also occur when the stability of the chest wall is lost—even if the pleura remains intact.

3. *Mediastinal flap or flutter*

A further handicap to efficient ventilation is a to-and-fro movement of the whole mediastinum. Oxygen lack and excess carbon dioxide stimulate the respiratory centre to produce exaggerated respiratory efforts. Such efforts in the presence of a mobile mediastinum result in a jerky flap or flutter of the mediastinum. It greatly embarrasses the circulation, resulting in a marked fall in blood pressure and rise in pulse rate; thereby is completed the vicious circle of anoxia.

II. *Disturbances due to Lack of Oxygen*

The cells in the vital centres of the medulla of the central nervous system and in the "specific tissue," as well as the ventricular muscle tissue of the heart, are those most vitally in need of a *continuously* adequate supply of oxygen.

III. *Disturbances due to Excess Carbon Dioxide*

Oxygen lack and excess carbon dioxide must be closely linked in all our thinking because the effects of each are very closely related and often overlap.

Gibbon (1950) and Etsten (1953) have concluded that the open pneumothorax and not the particular posture (whether lateral or prone) causes inadequate alveolar ventilation and consequently excessive retention of carbon dioxide.

All grades of respiratory acidosis during intrathoracic surgery have been reported (17).

IV. *Disturbances of Cardio-Circulatory Dynamics*

1. *Cardiac output*

(*a*) Inefficient spontaneous breathing as well as some types of pressure breathing may cause impairment of cardiac output (16, 18, 19).

(*b*) Cardiac handling and surgery may produce a low cardiac output with a fall in peripheral resistance, which responds to vasopressor drugs (20).

(*c*) Vasopressor drugs *per se* may lower the cardiac output (21).

(*d*) Inadequate blood replacement or excessive replacement may interfere with an adequate output of the heart.

Inadequate coronary blood flow may sometimes be directly improved by intra-aortic transfusion of blood.

2. *Cardiac arrhythmias*

During cardiac surgery, direct stimulation of the heart may be the cause of cardiac arrhythmias. These are most readily corrected by having the surgeon desist from constant handling of the heart (22).

Johnstone (23) has reported that retention of carbon dioxide is the cause of the ventricular arrhythmias associated with cyclopropane or pentothal anaesthesia. Such arrhythmias can occur in spite of good oxygenation.

3. *Cardiac arrest*

(*a*) *Cardiac standstill* may be defined as a very sudden failure of the heart to pump blood. It is many times more common than ventricular fibrillation (24). Reid thinks that there is a "trigger reflex mechanism" which eventually precipitates the condition but that there are various underlying causes. Of the latter, excess carbon dioxide is seriously incriminated, as well as lack of oxygen. In over 1500 cases of cardiac arrest, none were apparently adequately atropinized. We should consider cardiac arrest as an avoidable situation rather than one to be dramatized by spectacular therapy.

(*b*) *Ventricular fibrillation.* It is generally conceded that the prelude to ventricular tachycardia and fibrillation consists in the development of multiple ventricular extrasystoles.

Ventricular fibrillation is described (26) as an unco-ordinated type of contraction which produces no useful beats. There are typical "rippling" movements of the ventricular muscle which give the impression to the hand of a "bag of worms" (M. Thorek, Chicago).

The phenomenon of post hypercapnoeic ventricular fibrillation is a striking one. The relationship between potassium and hypercapnia is a fascinating study (27). Sealy *et al.* suggested that the rise in potassium levels after the cessation of hypercapnia *may* be due to a sudden release of epinephrine.

V. *Disturbances due to Posture* (15, 17)

1. Ventilatory
2. Problem of Secretions
3. Cardiac Function

VI. *Disturbances due to Reflexes*

Nosworthy (7) has emphasized the relative value of the stimulus and the threshold of irritability of the respiratory tract, indicating that the sensitivity increases at its lower levels—e.g., bronchial reflexes may remain acutely sensitive.

When a patient "reacts," the expiratory muscular effort against a spastic glottis or bronchospasm impedes the blood flow to the left auricle. This causes an immediate fall in cardiac output and a severe drop in systolic blood pressure. The pressure in the pulmonary artery and right ventricle increases, resulting in a rise in venous pressure, which makes distended veins and cyanosis in the "cape region" very noticeable to the anaesthetist.

(The significance of the cough reflex must never be forgotten.)

Many other reflexes are associated with vagal stimulation but their real significance in anaesthesia has not yet been proven.

VII. *Disturbances due to Loss of Body Heat* (11)

Even when all loss of blood, fluids, and electrolytes is made good, loss of body heat is a deciding factor in how much can be done inside the chest. Loss of heat is considerable when the chest wall is widely opened and the time factor is important.

Résumé

Les organs principaux du thorax, le cœur et les poumons fonctionnent en synergie et il est difficile de les considérer indépendamment. Leur fonction en cavité thoracique close est mieux connue de jour en jour et doit être mieux comprise avant qu'il soit possible de déterminer ce qui en perturbe la physiologie quand on ouvre et opère dans le thorax.

La fonction principale de cet ensemble cardio-pulmonaire est de fournir un apport constant d'oxygène et d'éléments nutritifs à toutes les cellules de l'organisme et aussi d'évacuer le dioxide de carbone et les dichets métaboliques.

Un échange gazeux efficace dans le poumon réquiert la fonction efficace de quatre principaux facteurs:

I. La ventilation, désignée par V; ou plus précisement la ventilation alvéolaire

II. La distribution, i.e., le mélange des gas dans le poumon

III. La diffusion

IV. La circulation

La ventilation alvéolaire (V) n'est pas seulement le premier et le plus important facteur mais aussi celui qui est le plus facilement modifié par l'anesthésiste et le chirurgien.

Les études actuelles au cours d'interventions thoraciques avec pneumothorax ouvert sout peu nombreuses. Il y a quartorze ans, Noseworthy décrivit clairement d'une façon classique avec tracés linéaires, les problèmes que pose l'ouverture du thorax.

Une ventilation alvéolaire efficace dans tout le sens de ce qu'elle implique devrait être le but de tout anesthésiste. Si elle est maintenue de façon constante, presque toutes les perturbations nuisibles énumérées plus bas pourront être évitées.

Perturbations physiologiques

I. Perturbations de la dynamique respiratoire
   1. Collapsus pulmonaire et déplacement du médiastin
   2. Respiration paradoxale
   3. Flutter mediastinal

II. Perturbations dues au manque d'oxygène

III. Perturbations dues à un excès de dioxide de carbone

IV. Perturbations de la dynamique cardio-vasculaire
   1. Débit cardiaque
   2. Arythmie cardiaque
   3. Arrêt cardiaque

V. Perturbations dues à la position du patient

VI. Perturbations dues aux reflexes

VII. Perturbations dues à des pertes de chaleur corporelle

REFERENCES

1. Björk, V. O. J. Thoracic Surg. *26*: 67 (1953).
2. Woodruff, W., Wright, G. *et al.* J. Thoracic Surg. *26*: 156 (1953).
3. Lucas, B. G. B. Anaesthesia *7*: 88 (1952).
4. Negus, V. E. Thorax *4*: 57 (1949).
5. Negus, V. E. Thorax *7*: 148 (1952).
6. Tremble, G. E. Personal communication (1954).
7. Nosworthy, M. D. Anaesthesia *3*: 86 (1948).
8. Briscoe, W. A. & McLemore, G. A., Jr. Thorax *7*: 67 (1952).
9. Herxheimer, H. Thorax *4*: 65 (1949).
10. Wright, G. Discussion of Reference 2 (1953).
11. Nosworthy, M. D. Proc. Roy. Soc. Med. *34*: 479 (1941).
12. Crafoord, C. Surg., Gynec. & Obst. *89*: 629 (1949).
13. Organe, G. S. W. Modern Practice in Anaesthesia. 2nd ed., p. 453 (1954).
14. Nosworthy, M. D. Anaesthesia *6*: 211 (1951).
15. Brown, A. I. P. Thorax *3*: 161 (1948).
16. Brown, A. I. P. & Sellick, B. A. Anaesthesia *8*: 4 (1953).
17. Etsten, B. E. J. Thoracic Surg. *25*: 286 (1953).
18. Saklad, M. J. Thoracic Surg. *28*: 31 (1954).
19. Etsten, B. E. *et al.* Anesthesiology *16*: 365 (1955).
20. Hale, D. E. Anesthesiology [text], p. 537 (1954).
21. Sarnoff, Stanley. Personal communication (1954).
22. Murray, Gordon. C.M.A.J. *68*: 227 (1953).
23. Johnstone, M. Anaesthesia *8*: 32 (1953).
24. Stephenson, H. E., Reid, L. C. *et al.* Ann. Surg. *137*: 731 (1953).
25. Reid, L. Corsan. Discussion of Reference 24, p. 742.
26. McMillan, I. K. R. & Cockett, F. B. Thorax *7*: 205 (1952).
27. Sealy, W. C. *et al.* J. Thoracic Surg. *28*: 447 (1954).

ANAESTHETIC TECHNIQUES AND THE "OPEN CHEST"*

RENÉ LÉTIENNE, M.D., F.R.C.P.(C)**

"OPEN CHEST" anaesthesia brings together so many factors, requirements and means to deal with them, that a presentation of definite opinions is hardly justified when considering proper anaesthetic techniques for surgical thoracic patients. Simple solutions to some complex problems have yet to be found, notwithstanding an abundance of available drugs, methods, and apparatus (1, 2).

Even after careful investigation and estimation, patients with seemingly adequate functional reserves will be encountered who are not fit to resist actual conditions of anaesthesia and stress. Their general condition will deteriorate rapidly during induction or soon after a lung is allowed to collapse, and they will not respond to ordinary corrective measures. The value of assessing vital functions in conscious patients (3), not submitted to the actions of depressant drugs, is inestimable, but the information is never so exhaustive as to make possible absolute competence for anaesthesia and its associated risks of hypoxia. It is also important to remember that, during the course of anaesthesia, unusual responses are frequent and that conventional treatment, based on studies of conscious patients, does not necessarily correspond or may not be sufficient (4).

With some knowledge of the proposed operation and the mode of performing it, watching its progress in detail greatly facilitates the task of both surgeon and anaesthetist, who should thoroughly understand each other's problems, so that control of ventilation, of secretions, of haemorrhage, of reflex activity will also provide for access to pathology, its exploration and treatment.

It is clear that normally the technique which the anaesthetist knows best and which he can most skilfully employ should be his logical choice. However, many will indulge (beginners probably being more prone to temptation) in a hodgepodge of anaesthetic acrobatics, under the impression that flashy performance, which cannot disguise a flagrant lack of clinical judgment and undigested theories, is evidence of worthy achievement. Unfortunately, the patient always pays a stiff price for such bluffing. Trifling with procedures which are too difficult to perform and which cannot remain under full control of the anaesthetist probably leads to more inefficiency than rigid adherence to blind routine. Variants of many procedures can be adopted but one must keep in mind the hazards to be overcome and avoid, if possible, techniques liable to jeopardize physiological equilibrium.

METHODS

General anaesthesia by the closed method is now commonly used. Regional methods have been supplanted because they do not allow enough regulation of the risks of an "open chest." Topical anaesthesia and local infiltration of sensory

*From a Panel Discussion on "Anaesthesia and the Open Chest," held, under the direction of Dr. S. M. Campbell, at the Annual Meeting of the Canadian Anaesthetists' Society in the Banting Institute of the University of Toronto, June 20, 21, and 22, 1955.

**Notre Dame Hospital, Montreal, Que.

and reflex zones contribute to safer anaesthesia. Familiarity and experience with surface analgesia would perhaps be more acceptable to anaesthetists at large if it is recognized that intubation of dyspnoeic patients or of "wet cases" is likely to be safer when performed correctly on conscious patients.

Agents

Selection of agents depends mainly on their pharmacological actions in relation to the patient's general condition, on the use of diathermy, and on the constant need for satisfactory oxygenation. In this latter respect, oxymetric studies have at least shown that the clinical eye is a poor judge of blood-oxygen saturation and that human organisms frequently exhibit an amazing resilience when submitted to oxygen famine. One notable adjunct in recent years has been the introduction of neuro-blocking drugs which decrease reflex activity during anaesthesia and possibly reduce postoperatively the incidence of atelectatic complications of neuro-vegetative origin. The protective mechanisms of cough and consciousness should return with the termination of the operation as they remain, by far, the least traumatic and the most efficient means of securing broncho-pulmonary toilet and satisfactory expansion of the lung tissue. Bronchoscopy is a possible necessity immediately before, during, or after operation and equipment for bronchoscopy and aspiration should always be available. It may be mandatory before surgery for very wet cases or for those suffering from severe thoracic injuries. If at all feasible, it should be performed under topical analgesia, the dangers of bronchoscopy under general anaesthesia being only too well known. Should the procedure be protracted and the patient be in a state of exhaustion, it is safer to postpone surgery as attempts to induce general anaesthesia may be extremely risky.

Equipment

The imposing array of equipment used in conjunction with thoracic anaesthesia is made necessary because it is difficult to satisfy simultaneously the exigencies of physiology, of dynamics, and of anatomy.

Several important considerations appear in combination: prevention of paradoxical breathing and mechanical flap, of coughing and bucking, and of pathogenic spreading, while allowing for adequate gaseous exchange and aspiration of bronchial fluids. These requisites must be satisfied without undue perturbations of the cardiovascular function, without initiating autonomic reflex phenomena, and under an even plane of anaesthesia which will also allow for rapid recovery.

The use of endotracheal tubes is indispensable in "open chest" anaesthesia, even if they sometimes cause damage to tracheal structures and are a frequent source of noxious reflexes. The importance of this autonomic hyperactivity has been somewhat exaggerated at times (5), the E.C.G. changes especially, because of their fleeting character and because it is now possible to regulate them by nerve-blocking methods. Certainly, they do not take precedence over respiratory safety and control.

Desirability for a leak-proof airway has led to the use of large-bore tubes, pharyngeal packs, and inflatable cuffs. Trans-thoracic operations not involving

the air passages directly are now commonly performed with the assistance of cuffed endotracheal tubes, as are operations for lung surgery of the "dry type." Exceptions are mainly in the case of air cysts of the lungs, gross anatomical deformities and, of course, with children.

In "wet cases," it must be realized that cuffed tubes may act as a dam to retain bronchial fluids between the catheter and the tracheal wall, with a risk of directing the overflow of secretions into another lobe or lung. Beecher (2), in a very convincing way, favours the use of intermediate-sized tubes which lie free under an ordinary face mask for total or partial lung resections, relying on posture and suction to check secretions and spread of disease from healthy tissue (Figure 1).

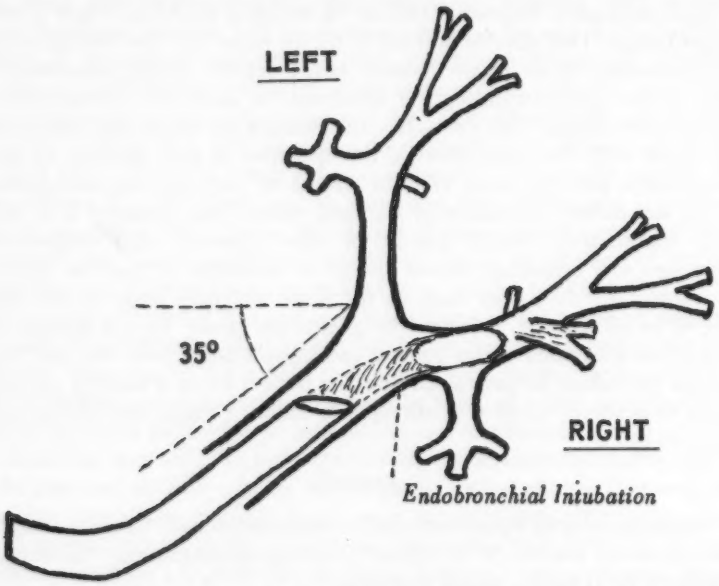

FIGURE 1. Left Thoracotomy in lateral position: gravity drainage. A 10° tilt is adequate in the prone (Overholt) position.

The case against systematic use of inflatable cuffs is obvious and sound reasons only warrant their use. Likewise, when control of secretions and ventilation stands as a major problem from the anaesthetic point of view, justification for the use of other methods should logically be subordinate to the greater advantages which these can actually procure.

If postural drainage and suction associated with endotracheal techniques are deemed insufficient for particular cases, separate lung anaesthesia or segmental blocking permitting drainage or inflation of localized pulmonary areas can prove most convenient. But the multitude of methods advocated to achieve satisfactory endobronchial anaesthesia is a fair gauge of their present status in respect to efficacy and practicability. This does not mean that these techniques are to be neglected, for, when they are indicated and feasible, they definitely add to the safety of certain operations, specifically in the presence of broncho-pleural fistula,

of copious suppuration, of pulmonary cysts, or for pneumonectomies or lower lobe resections. For upper lobectomies or where anatomical abnormalities exist, such procedures are still not consistently satisfactory, even in the hands of the very skilled.

Unilateral bronchial intubation of the main bronchus of a healthy lung and bronchial tamponage are now seldom performed on account of their many shortcomings. Bronchial occlusion with a cuffed suction catheter of the Thompson or the Magill type is theoretically ideal both from an anaesthetic and from a surgical angle, but it is difficult to perform (Figure 2). A blocker can easily slip out of

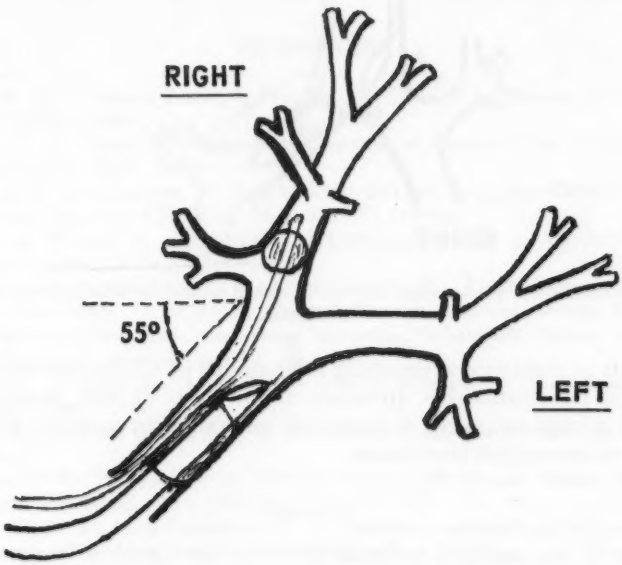

FIGURE 2. Gravity drainage for right thoracotomy. This extreme position is not necessary with bronchial block and suction.

place; because it is separate from the endotracheal tube and placed alongside of it, an air-tight fit may not be obtained. An endotracheal tube incorporating an endobronchial blocker, devised by Sturtzbecher (6), assures a more leak-proof system but, otherwise, this modification presents the same disadvantages and middle or upper blocking remains even harder to carry out.

Carlens' endobronchial tube (7) is probably the best answer to this singularly intricate problem (Figure 3). Its introduction is not too exacting for the patient or the anaesthetist; it is adaptable to most cases where its use could be advantageous and serves well the purposes of one-side anaesthesia, since it makes possible segmental inflation and deflation, or suction, while an even, uninterrupted plane of anaesthesia is maintained. It also provides a rather easy way to adapt one's task to surgical requirements. The aerodynamic properties of this double-lumen tube have been studied (8, 9) under various circumstances and results of

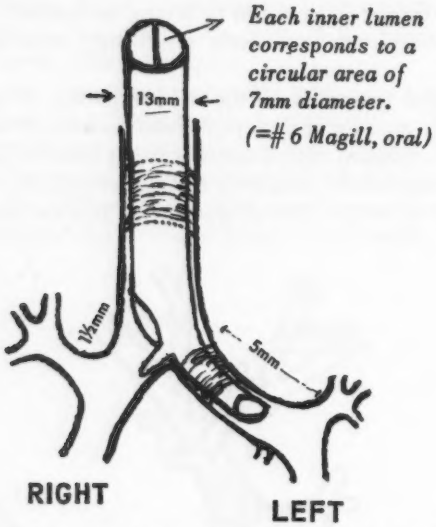

FIGURE 3. Carlens' tube permits bilateral bronchial control for isolation, suction, and insufflation.

experiments on resistance to breathing indicate that its routine use for all thoracic cases might be questionable. However, at low rates of flow, resistance to air passage is greatly minimized if controlled respiration is used and physiological disturbances are negligible or absent.

SUMMARY

Solution of the manifold technical problems associated with anaesthesia for "open chest" surgery depends primarily on a thorough understanding of the physiological and mechanical aspects involved. Too strict adherence to any standardized routine may spell failure if each patient and each surgical demand are not clearly recognized by each anaesthetist.

Endotracheal and endobronchial general anaesthesia have displaced other methods. Drugs and equipment to carry out these techniques are numerous but are of limited assistance in providing a perfect answer to meet the challenge. The arm-chair or the floor-walker type of anaesthetist stands to gain immeasurably in experience and skill by close study and minute-to-minute observation of patients submitted to this form of anaesthesia.

RÉSUMÉ

A cause des nombreux problèmes de physiologie, de dynamique et d'anatomie qu'elle soulève, il n'est pas facile de trouver une formule simplifiée si l'on considère les techniques anesthésiques employables en chirurgie thoracique transpleurale. L'anesthésie générale, par voie endotrachéale ou endobronchique, a

supplanté les autres méthodes, parce qu'elle permet un meilleur contrôle des perturbations physio-pathologiques et des risques inhérents à ces interventions. L'anesthésie endotrachéale suffit dans l'immense majorité des cas. Où il y a danger de contamination ou d'inondation des voies respiratoires, les méthodes endobronchiques s'imposent plus particulièrement, surtout au moyen du tube Carlens.

Drogues, méthodes et appareillage n'ont d'importance qu'en autant qu'ils sont utilisés à bon escient, par un anesthésiste sérieux et expérimenté. Les techniques destinées à épater les badauds, mais qui dépassent l'habilité de ceux qui s'amusent à s'en servir, taxent injustement l'opéré et n'ont aucun droit de cité.

REFERENCES

1. Mushin, W. H. & Rendell-Baker, L. Principles of Thoracic Anaesthesia. Springfield, Ill.: C. C. Thomas (1953).
2. Beecher, H. K. Principles, Problems, and Practices of Anesthesia for Thoracic Surgery. Springfield, Ill.: C. C. Thomas (1952).
3. Comroe, J. H. & Blackmore, W. S. The Diagnostic and Prognostic Value of Pulmonary Function Tests. Surg. Clin. North Amer. *29*: 1671 (1949).
4. Fisher, K. & Winsor, T. Contributions of Electrocardiography to Anesthesia for Chest Surgery. Anesthesiology *13*: 147 (1952).
5. Converse, J. G., Landmesser, C. M. & Harmel, M. H. Electrocardiographic Changes during Extubation: A Study of Electrocardiographic Patterns during Endotracheal Anesthesia including those seen during Intubation, Endotracheal Suction, and particularly Extubation. Anesthesiology *13*: 163 (1952).
6. Oech, S. R. A Cuffed Endotracheal tube with an Incorporated Endobronchial Blocker. Anesthesiology *16*: 468 (1955).
7. Bjork, V. O., Carlens, E. & Fribuc, O. Endobronchial Anesthesia. Anesthesiology *14*: 60 (1953).
8. MacKrell, T. N. Resistance study with the Carlens-Stille Double Lumen Endotracheal Catheter. Anesthesiology *15*: 209 (1954).
9. Orkin, L. R., Siegel, M. & Rovenstine, E. A. Resistance to Breathing by Apparatus used in Anesthesia. Anesth. & Anal. *33*: 217 (1954).

THE USE OF MECHANICAL CONTROL OF RESPIRATION IN ANAESTHESIA FOR THE OPEN CHEST*

W. N. ROLLASON, M.B. (Birm.), M.R.C.S., F.F.A.R.C.S., D.A. (Eng.)**

THE PRESENT EMPLOYMENT of automatic devices for rhythmic inflation of the lungs and the use of controlled respiration and curare to solve the problems of surgical pneumothorax merit tribute to the pioneer work of Green and Janeway nearly half a century ago, and to the far-sighted suggestions of Brat and Schmieden (1).

When controlled respiration is performed by a machine the information derived by the anaesthetist from the feel of the bag during inflation is lost. This includes the depth of anaesthesia, the completeness of curarization, the presence or otherwise of conditions like bronchospasm, respiratory obstruction, and accumulation of secretions; the volume exchange that occurs when the bag is squeezed with a particular manual effort; the detection of every flicker of the diaphragm and every embryo cough; the observation of the volume changes due to the heart beat transmitted to the bag between inflations and the lessened resistance to ventilation from the relief of pulmonary congestion following successful mitral valvotomy or from excision of a portion of calcified pericardium or decortication of a lung.

Furthermore, unless the machine is "patient triggered," curarization should be complete, although in this state the patient's energy can be conserved and oxygen consumption lowered by 10 per cent. Cardiac output may be reduced, especially at the peak of each inspiration, but this can be offset if the duration of inspiration does not exceed 1.5 sec., the inspiratory peak pressure does not exceed 25 cm. of water and is rapidly reduced to atmospheric, and the respiratory rate does not exceed 16–20 per minute. In this way neither circulation nor ventilation need be imperilled, provided the machine is capable of delivering 40–60 litres of air per minute, and this is important to the severely ill patient.

Again, hyperventilation might result and lower the CO_2 content thus raising the pH of the blood. Experimental observations, however, show this to be extremely unlikely with an open chest (3), and apnoea is probably largely due to inhibition of the Hering Breuer reflex as a result of rhythmic distension of the lungs.

There may be difficulty in assessing the depth of anaesthesia when the patient is apnoeic, but this matters little when nitrous oxide with adequate oxygen is the anaesthetic, and with these agents diathermy can be used inside the chest.

Lastly, there may be a danger of further impacting plugs of sputum into the bronchi.

Nevertheless, mechanical control does set free the hands of the anaesthetist working alone and enables him to perform other tasks. These include the setting

*From a Panel Discussion on "Anaesthesia and the Open Chest," held, under the direction of Dr. S. M. Campbell, at the Annual Meeting of the Canadian Anaesthetists' Society in the Banting Institute of the University of Toronto, June 20, 21, and 22, 1955.

**Consultant Anaesthetist to Hull A & B Groups, Hull, England.

up of transfusions and maintenance of a constant blood volume during the operation. This is particularly important in pneumonectomy where fluid replacement must be adequate and overloading avoided.

Repeated blood pressure and pulse readings are essential to the proper management of any intrathoracic operation and particularly so when hypotensive and hypothermic techniques are employed. In the latter a constant watch must also be kept on the rectal or oesophageal temperature and on the electrocardiogram.

Furthermore, mechanical control relieves the physical fatigue of the anaesthetist's hands and arms during long cases. Manual control tends to fall short of efficiency particularly if alternating positive and negative pressures are attempted, as, for instance, with a Coxeter Mushin machine.

Again, by maintaining a regular respiratory rhythm and constant pressure mechanical control enables the "differential pressure" respiration technique described by Esplen to be carried out more effectively than by hand (4). In this technique the lung which has remained collapsed can be re-inflated without difficulty at the end of the operation even though this lasts several hours. No postoperative complications and no respiratory acidosis have ensued. The differential effect, however, cannot be properly demonstrated when multiple cavities or emphysematous changes are present in the lung on the operated side nor when an A.P. or extensive lung disease is present on the contralateral side.

Lastly, some automatic respirators provide a negative pressure phase. This gives an adequate tidal volume with a smaller positive pressure during inspiration and is of value in reducing the right to left shunt when respiration is controlled in Fallot's Tetralogy and in aiding the circulation by ensuring an adequate venous return in those cases where it is impaired, such as conditions of shock, hypovolaemia, and cardiac decompensation. A slight head-down tilt can further assist this venous return. With negative pressures of —4 to —6 cm. of water mediastinal movement is very slight for all respiratory activity is abolished by completely satisfying the respiratory requirements of the patient. The machines described by Pinson (5), Mørch (6), Esplen (7), and Mortimer (8) all provide a negative phase; the Jefferson ventilator which is used on this continent is capable of providing negative pressures up to 10 cm. of water; and the new Blease machine which is now being manufactured in England provides negative pressures up to 7 cm. of water (9).

As a result of an experimental study of pulmonary histopathology in dogs with open chests following positive and negative pressure respiration, the conclusion was drawn that the most favourable endotracheal pressure allowing effective pulmonary ventilation with minimal lung damage was 15–20 cm. of water positive pressure and 5 cm. of water negative pressure (10).

Blood pressure in the superior vena cava in dogs has been directly measured by the use of an electrically recording stream bristle flowmeter; in the open chest, while positive pressure lung inflation impeded venous return, the interposition of a negative phase between positive pressure lung inflations did not benefit the circulation significantly (11).

On the other hand, in a human subject undergoing pneumonectomy the cardiac output calculated from the indirect Fick principle fell to 2.68 litres per minute

during anaesthesia with assistance by a prolonged phase and rose to 5.34 litres per minute during anaesthesia where there was assistance with both inflation and deflation (12).

No deleterious effects have been noted during or following operations where a negative phase of up to 5 cm. of water has been employed.

In addition, however, to providing a negative phase the modern mechanical automatic respirator should guarantee the following:

1. It should measure and be able to reproduce a certain tidal volume, which should not fall below 350 cc. in the adult (13).

2. It should be sensitive to pressure changes within the chest so that "cycling" (i.e., change from expiratory to inspiratory phase and vice versa) occurs at a peak pressure.

3. The inspiratory pressure should be variable from atmospheric to a maximum of 30 cm. of water, the higher pressure being required for inflation of the lungs on closure.

4. Inspiratory and expiratory phases must be variable so as to simulate the normal respiratory pattern of a fairly rapid initial flow, tailing off as the alveoli fill and exchange takes place, with a quick return to atmospheric or sub-atmospheric pressure on expiration; the wide range of control makes the respirator suitable for use with children as well as adults.

5. It should be possible to hold the lungs inflated at will and at varying pressures.

6. It should be possible to switch over to spontaneous respiration if desired.

7. There should be a mechanism for switching over to a rebreathing bag for manual control in cases of failure of the mechanism of the machine.

8. There should be a spill valve to enable the machine to be used with nitrous oxide and oxygen anaesthesia and an efficient humidifier incorporated when these gases are used.

9. There should be a means of holding a small positive pressure up to 5 cm. of water at the end of expiration.

10. The machine should be adaptable to any technique of anaesthesia and should be explosion proof.

The new Blease machine is probably the most highly developed piece of equipment of its type at present available and meets all these requirements.

In conclusion, however, I would stress that the automatic respirator, valuable though it can be, is only an ancillary aid. It is no substitute for keen clinical observation or constant vigilance, and as there is valuable information and delicate control which can only be imparted by the sensitive and skilled human hand, a technique combining manual and mechanical methods is the most useful in practice.

RÉSUMÉ

Lorsqu'il contrôle la respiration mécaniquement, l'anesthésiste est incapable de connaître le profondeur de l'anesthésie, le degré de relâchement musculaire et aussi, la présence d'obstruction respiratoire due soit a un bronchospasme soit aux sécrétions, ou encore, les variations de résistance dépendant de la congestion pulmonaire.

Il y a aussi le danger d'interférence avec le remplissage et l'évacuation cardiaques par suite de la régulation inadéquate des pressions, de l'air courant et de la longueur du cycle respiratoire.

Le contrôle mécanique libère l'anesthésiste et lui permit d'utiliser ses mains pour d'autres tâches. De plus, s'il est bien régularisé, il produit une ventilation plus efficace. Avec l'addition d'une phase négative allant jusqu'à 5 cm. d'eau dans les appareils les plus modernes, le débit cardiac est augmenté.

Le respirateur automatique moderne doit être capable de mésurer et de produire un volume requis d'air circulant de pas moins de 350 cc. chez l'adulte. Il doit pouvoir produire une pression positive allant jusqu'à 30 cm. d'eau lors de l'inflation du poumon quand on ferme un thorax. Les phases inspiratoires et expiratoires doivent être de contrôle facile de façon à être adaptable aux enfants aussi bien qu'aux adultes. Il devrait être possible de passer sans difficulté soit au contrôle manuel soit à la respiration spontanée. Il faut qu'il puisse servir pour tous les types d'anesthésie. Il ne devrait pas y avoir danger d'explosion.

Un respirateur mécanique doit être considéré seulement comme un adjuvant et non un substitut de l'observation clinique et de la vigilance constante.

REFERENCES

1. Mushin, W. W. & Rendell-Baker, L. Principles of Thoracic Anaesthesia. Oxford: Blackwell (1953).
2. Spalding, J. M. K. Lancet, May 28: 1099 (1955).
3. Lucas, B. G. B. & Milne, E. H. Proc. Roy. Soc. Med. *46*: 368 (May 1953).
4. Esplen, J. R. Brit. J. Anaesthesia *23*: 214 (October 1951).
5. Pinson, K. B. Anaesthesia *4*: 79 (April 1949).
6. Mørch, E. Trier. Anaesthesia *3*: 4 (January 1948).
7. Esplen, J. R. "The Fazakerley Respiratory"; Personal communication.
8. Mortimer, P. L. F. Anaesthesia *9*: 312 (October 1954).
9. Blease, J. H. Personal communication.
10. Waltz, R. C. *et al.* Surg., Gynec. & Obst. *99* (November 1954).
11. Hubay, C. A. *et al.* Anesthesiology *15*: 445 (September 1954).
12. Allbritten, F. F., Jr., *et al.* Ann. Surg. *140*: 576 (October 1954).
13. Harbord, R. P. *et al.* Proc. Roy. Soc. Med. *46*: 367 (May 1953).

NEWS LETTER

British Columbia Division

Dr. E. A. Pask, Professor of Anaesthesia, Durham University, Newcastle-on-Tyne, recently visited Vancouver and spoke to the members of the British Columbia Division on "Anaesthetic Problems in Myasthenia Gravis."

°

Dr. H. B. Graves, Director of Anaesthesia, Vancouver General Hospital, visited many anaesthetic centres in Belgium, France, Switzerland, and England after attending the meeting of the World Federation of Societies of Anesthesiologists in Scheveningen, Holland.

Saskatchewan Division

A course of instruction in oxygen therapy has started at the University Hospital, Saskatoon, for nurses and orderlies. Instruction is being carried out by the Department of Anaesthesia.

Dr. Max S. Sadove, University of Illinois, gave a talk on the "Management of Acute Poisoning" during his visit to Saskatoon on Wednesday, October 5th.

°

Dr. E. Asquith spoke on "Anaesthetic Management for the Rural Practitioner" on October 19th at Regina, during the Saskatchewan Medical Convention.

°

Dr. A. B. Dobkin will read a paper entitled "Chlorpromazine" at the 13th Annual Congress of Anesthetists, Miami Beach, Florida, April 9–12, 1956.

°

Dr. A. Henschel, Saskatoon, has been invited to read a paper on "Posture and Clinical Anaesthesia" at the same meeting.

Manitoba Division

Dr. Max Sadove, University of Illinois, presented a paper on "Anaesthesia for Cardio-Vascular Surgery" at the monthly meeting of the Manitoba Division, October 4, 1955. Following this, Dr. Sadove encouraged a question and answer period during which he answered all questions that were asked in an admirable manner. The meeting was well attended by a record turnout of enthusiastic members.

°

Dr. Bernadine Roe announced her engagement to Mr. John Ristall, the wedding to take place in Winnipeg, in November 1955.

°

Dr. Marcia and Dr. Angus Wood (Winnipeg General Hospital) announced the birth of their daughter Sherry Louise on July 24, 1955.

Dr. Jim Daniels has joined the St. Boniface Anaesthetic Group. He was associated with Dr. Alan Noble in Kingston, Ontario, in 1953.

Ontario Division

On Saturday, October 22, 1955, the Ontario Division of the Canadian Anaesthetists' Society combined with the Section on Anaesthesia of the Ontario Medical Association to hold a meeting at Windsor, Ontario. Several of the surgical staff and many of the general practitioners doing part-time anaesthesia in the Windsor area hospitals increased the attendance to 75.

The Nursing Staff of the Hôtel Dieu Hospital extended their hospitality by allowing the use of their fine lecture hall and served coffee and doughnuts at the morning and afternoon breaks.

A luncheon was arranged at Mario's Restaurant and an opportunity provided for many questions to be asked the speakers of the morning session. The programme was as follows:

Cardiac Arrest	Dr. R. Orange, Sudbury
Aspiration Bronchoscopy	Dr. Bruce Proctor, Wayne University, Detroit
Cortisone and ACTH in relation to the Anaesthetists	Dr. J. K. Moss, Dr. D. Best, and Dr. V. L. Politi, Hamilton
Intravenous Anaesthetics	Dr. Paul Dumke, Ford Hospital, Detroit
Use of Dextran	Dr. Murray Young, Connaught Laboratories, Toronto
Nitrous Oxide Anaesthesia	Dr. Fred Clements, Toledo, Ohio
Re-evaluation of Spinal Anaesthesia	Dr. William MacKersie, Grace Hospital, Detroit.

°

Dr. Geoffrey Organe, of the Westminster Hospital, London, England, Secretary of the World Federation of Societies of Anesthesiologists, lectured to the postgraduate course in Anaesthesia at the University of Toronto in November 1955.

Nova Scotia Division

Monthly meetings of the Nova Scotia Division have resumed; they are held the third Monday evening of the month at the Victoria General Hospital.

°

Dr. C. Henderson, having completed his postgraduate training in Anaesthesia at the Victoria General Hospital, Halifax, has returned to his native Newfoundland and is practising anaesthesia in St. John's.

°

Dr. A. S. Wenning presented a paper on "Hazards of Paediatric Anaesthesia" to the annual Nova Scotia Medical Society's Refresher Course in October.

A two-day Regional Meeting for the Maritimes was held at the Victoria

General Hospital, Halifax on November 7 and 8, 1955. The programme was as follows:

Anaesthesia for Cardiac Surgery

Monday, November 7, 1955

2.00 P.M. Anatomy, Histology and Embryology of Cardiac Abnormalities
Dr. R. W. BALLEM

3.00 P.M. Medical Aspects of Cardiac Abnormalities
Dr. D. L. ROY

8.00 P.M. Open Meeting: Anaesthesia for Cardiac Surgery
Dr. S. M. CAMPBELL, Professor of Anaesthesia, University of Toronto

Tuesday, November 8, 1955

2.00 P.M. Physiology of Cardiac Disease
Dr. C. B. WELD

3.00 P.M. Pharmacology of Cardiac Drugs
Dr. J. G. ALDOUS

4.00 P.M. Clinical Assessment and Preoperative Therapy
Dr. L. C. STEEVES

8.00 P.M. Open Meeting—Nova Scotia Division: Anaesthesia for Cardiac Patients requiring General Surgery
Dr. S. M. CAMPBELL, Professor of Anaesthesia, University of Toronto

•

WORLD CONGRESS OF ANESTHESIOLOGISTS

Canadian Anaesthetists who attended the World Congress of Anesthesiologists held at Scheveningen, Holland, September 1955, were: Dr. H. B. Graves, Vancouver; Dr. Neil A. Stewart, Vancouver; Dr. Kathleen Langston, Vancouver; Dr. Mary A. Nicholson, Saskatoon; Dr. Gordon Wyant, Saskatoon; Dr. H. J. Shields, Toronto; Dr. S. M. Campbell, Toronto; Dr. R. A. Gordon, Toronto; Dr. J. S. Heron, Toronto; Dr. Norman McNally, Ottawa; Dr. H. R. Griffith, Montreal; Dr. Eugene Allard, Quebec; Dr. B. Paradis, Sillery; Dr. R. Brault, Sillery.

•

CANADIAN ANAESTHETISTS' SOCIETY

ANNUAL MEETING, 1956

The Annual Meeting for 1956 will be held at Mont Tremblant Lodge, Mont Tremblant, Quebec, June 18, 19, and 20.

WESTERN DIVISIONS MEETING

A Regional Meeting of the Western Divisions, Canadian Anaesthetists' Society, will be held in Vancouver, British Columbia, under the auspices of the British Columbia Division on April 5, 6, and 7, 1956.

WORLD FEDERATION OF SOCIETIES OF ANESTHESIOLOGISTS

At the first meeting of the General Assembly of the World Federation of Societies of Anesthesiologists the following officers were elected:

President

Dr. Harold R. Griffith (Canada)

Vice-Presidents

Dr. C. R. Ritsema van Eck (Netherlands)
Dr. A. Goldblat (Belgium)
Dr. R. Frey (Germany)
Dr. M. Corbelo (Cuba)

Secretary-Treasurer

Dr. Geoffrey Organe (England)

Executive Committee

Dr. J. Boureau
Dr. E. Ciocatto
Dr. J. Gillies
Dr. A. Goldblat
Dr. T. Gordh
Dr. A. Gonzales Varela
Dr. R. A. Gordon
Dr. H. R. Griffith
Dr. N. R. James
Dr. O. Mayrhofer
Dr. R. P. W. Shackleton
Dr. Zairo Vieira

At a meeting of the Executive Committee on September 10, 1955, Dr. A. Goldblat was elected as Chairman and Dr. C. R. Ritsema van Eck and Dr. S. G. Talwalkar were co-opted to the Executive Committee.

It was also agreed by the Executive Committee that the Second General Assembly should take place during a Congress to be arranged for 1960.

THE ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA

Examination Results

The following candidates in the Specialty of Anaesthesia successfully completed the qualification shown at the Examinations of the Royal College of Physicians and Surgeons of Canada in November and December, 1955.

Fellow of the Royal College of Physicians of Canada

Parsons: George Vandenoff	78 Henry St., Moncton, N.B.
Power, David John	St. Mary's Hospital, Montreal. P.Q.
Smith, Albert Owen Code	30 Elm Avenue, Toronto, Ont.

Certificate Specialists in Anaesthesia

Aavik, Imbi	74 St. Mary St., Suite 201, Toronto 5, Ont.
Archambault, Jean	516 est, rue Beaubien, Montréal, P.Q.
Atnikov, Murray Gerald	559 E. 12th Avenue, New Westminster, B.C.
Bardeen, Ann	University Hospital, University of Saskatchewan, Saskatoon, Sask.
Blair, John Harold	51 Greenbrook Drive, Toronto 9, Ont.
Cheng, Ming-Chu	Royal Victoria Hospital, Montreal, P.Q.
Day, George Frederick	829 West Broadway, Vancouver 9, B.C.
Dobkin, Allen Benjamin	Dept. of Anaesthesia, University of Saskatchewan, Saskatoon, Sask.
Dobson, Joseph Arthur	106 Alma St., Moncton, N.B.
Edwards, Kenneth Frederick	169 Hillendale Ave., Kingston, Ont.
Esdale, William Leonard	1601 Vista Manor, 319 North Tacoma Ave., Tacoma 3, Wash., U.S.A.
Firth, John Daniel Archibald	Dept. of Anaesthesia, Montreal Neurological Institute, University St., Montreal, P.Q.
Foster, Norman Edward	117 Superior Ave., Calgary, Alta.
Freund, Gertrude	1598 Bathurst St., Toronto, Ont.
Gillies, Deirdre May Macleod	Hôpital Notre-Dame de l'Espérance, 1275 Côte Vertu, Ville St-Laurent, P.Q.
Grout, Philip Daniel	58 Greenbrook Drive, Toronto 9, Ont.
Henderson, Charles Urquhart	6 Glenview Terrace, P.O. Box 379, St. John's, Nfld.
Holden, Charles Patrick	Dept. of Anaesthesia, Queen Mary Veterans Hospital, Montreal, P.Q.
Kay, Harold Tutt	67 Aylmer Ave., Ottawa, Ont.
Laporte, Jean	10441, rue Hamel, Montréal, P.Q.
LeBlanc, Jean-Jacques	137, rue Laurier, Hull, P.Q.
Lefebvre, Roger	6412, rue Briand, Montréal, P.Q.
Levin, Samuel Robert	641 St. Mary's Road, St. Vital, Winnipeg 8, Man.
Mackay, Joseph Alastair	2301 Emerson Ave. N., Minneapolis, Minn., U.S.A.
Macphail, Hugh Rose	11563, 80th Ave., Edmonton, Alta.

MATE, Maria	No. 8, 1360 Burnaby St., Vancouver, B.C.
MCALPINE, Douglas Fraser	2939 College Ave., Regina, Sask.
MCCAUGHEY, Thomas Joseph	Associated Anaesthetists of Winnipeg, 4th Floor West, Winnipeg General Hospital, Winnipeg, Man.
MCDONALD, Alexander William	105 Jarvis St., Cornwall, Ont.
MOSS, John Kitchener	Highland Mills, Dundas, Ont.
NATSUK, Antony William	301 Carpathia Rd., Winnipeg 9, Man.
OATWAY, William Arthur	266 Cameron St., Moncton, N.B.
OULTON, John Leys	204 Elm Ave., St. Lambert, Montreal 23, P.Q.
RUSSELL, Earl Stuart	86 MacDonnell St., Kingston, Ont.
SCHULTZ, Maxwell Howard	829 West Broadway, Vancouver 9, B.C.
SCOTT, Norman Andrew	478 Albertus Ave., Peterborough, Ont.
SHYKOFF, Henry Jack	1097 Victoria Park Ave., Toronto, Ont.
STEVENSON, Isabel Cooper MacIntyre	Calgary General Hospital, Calgary, Alta.
TAYLOR, William Alan	2170 Lincoln Road, Windsor, Ont.
WOLKENSTEIN, Christopher Francis	c/o Mlles Ricard, 1700 Sherbrooke St. E., Montreal, P.Q.
WOOD, Marcia	Associated Anaesthetists of Winnipeg, 4th Floor West, Winnipeg General Hospital, Winnipeg, Man.

OBITUARY

George Douglass Stanley

Dr. George Douglass Stanley, one of Alberta's pioneer doctors, died in February, 1954, at the age of 78. Born in Exeter, Ontario, he attended Stratford Model School and later the University of Toronto, graduating in Medicine in 1901. Dr. Stanley started his practice at High River and later moved to Calgary. One of the six founders of the Calgary Associate Clinic, he was also chairman of the medical staff at both the Holy Cross and the General Hospitals. He was a member of the Board of Governors of the University of Alberta. The gymnasium at Mount Royal College was named in his honour. From 1913 until 1922 he represented the High River riding in the Legislative Assembly and from 1930 to 1935 was the Conservative member for Calgary East. Dr. Stanley was made an honorary life member of the Canadian Medical Association in 1950. He was made an Honorary Member of the Canadian Anaesthetists' Society in 1951. Author of several medical articles, he also wrote a book about his younger days in Alberta, entitled "Fun in the Foothills." In 1951, Dr. Stanley was awarded an honorary LL.D. from the University of Alberta for his contribution to Canadian life. He is survived by one daughter.

CANADIAN ANAESTHETISTS' SOCIETY

ANNUAL MEETING

MONT TREMBLANT LODGE

QUEBEC PROVINCE

JUNE 18, 19, 20, 1956

In the beautiful Laurentians

at the best possible time of year

• **PLAN NOW TO ATTEND** •

L.A. GASES
- Oxygen
- Nitrous Oxide
- Cyclopropane
- Helium
- Carbon Dioxide
- Mixtures

McKESSON
- Oxygen Tents
- Anæsthetic Machines
- Suction Pumps
- Resuscitators and Inhalers
- Metabolors

L.A.
- Flowmeters
- Pipeline Outlet Equipment

FOREGGER
- Cabinet and Portable Model Anæsthetic Machines
- Inhalator Equipment
- Endotracheal Equipment, Etc.

AIRCO
- Therapy Regulators
- Humidifiers

LOOK AHEAD WITH L.A.

L.A. hospital bulk oxygen installation.

L.A. hospital pipeline systems put "gas on tap" for oxygen therapy or emergency use.

L.A. GASES and EQUIPMENT

Whatever your hospital requirements — medical gases, anaesthetic or therapy equipment, or oxygen pipeline systems — Canadian Liquid Air is "there when needed" . . . ready to supply you, at short notice, from its nationwide distribution network, including numerous plants, branches and depots throughout the country.

L.A. offers *complete* service to hospitals . . . plus the prompt attention of specially trained technical representatives whenever expert advice or repairs are needed.

Close-to-home service, unexcelled quality of products, technical "know-how," and other advantages are yours when dealing with L.A.

MEDICAL GAS DIVISION

Canadian **LIQUID AIR** Company
LIMITED

BRANCHES, PLANTS, WAREHOUSES AND DEALERS IN ALL PRINCIPAL CENTRES OF THE NATION

CANADIAN ANAESTHETISTS' SOCIETY
APPLICATION FOR MEMBERSHIP

Name _____

Address _____

Education (Universities only—Dates and Degrees) _____

_____

_____

Internships _____

_____

_____

Post-Graduate Training in Anaesthesia (Location and Dates) _____

_____

_____

Specialist Qualifications in Anaesthesia (state Dates and if by Examination or otherwise) _____

_____

Appointments in Anaesthesia (Past and Present—Full Time or Part Time) _____

_____

Professional Memberships _____

Are you a member of the Canadian Medical Association? _____

Publications (Please attach list if necessary) _____

_____

Signature of Applicant _____

Proposed by _____

Seconded by _____

Fees: Certified Specialists—$20.00 per annum.
Other Members—$15.00 per annum.
Members Elect (Residents in Anaesthesia)—$1.00 per annum.

Please make cheques payable to:
"The Canadian Anaesthetists' Society"
and forward to
Secretary-Treasurer—516 Medical Arts Bldg., Toronto, Ont.

INDEX OF ADVERTISERS

THE CANADIAN ANAESTHETISTS' SOCIETY JOURNAL

Editorial Policy

The Canadian Anaesthetists' Society Journal is published quarterly by the Canadian Anaesthetists' Society Inc. Original articles are accepted for publication on the understanding that they are contributed exclusively to this journal and become the property of the Canadian Anaesthetists' Society. Articles are subject to such alteration as the Editor in his absolute discretion may deem necessary, but no major alterations will be made without consent of the Author.

Manuscripts

Articles should be typewritten in double space on one side of the paper only. Pages must be serially numbered, and each page should carry at its head the name of the author and the title of the article in full or in an appropriate abbreviation. The article should be concluded by a summary which will be intelligible without reference to the main text. All articles should be accompanied by a résumé presenting the important features in short form, for translation into the French language. French-speaking authors should provide this résumé in the French language.

References to the literature should be clearly indicated in the text by arabic numerals in brackets, thus (4). They should be set out in numerical order at the end of the article, typed in double space, as follows:

4. Griffith, H. R. & Johnston, G. E. The Use of Curare in General Anaesthesia. Anesthesiology 3: 481 (1942).

References to books will state in order: Name of Author, Title of Book, Edition, Place of publication, Publisher, Year of Publication, such as:

Labat, G. Regional Anesthesia. 1st ed., Philadelphia: Saunders (1922).

The names of all authors will be given in the first instance in each reference. In further references to the same authors the abbreviated form "Griffith *et al.*" may be used.

Illustrations

Photographs should be unmounted glossy prints. Drawings and charts should be in black India ink on white paper. Reproductions in colour will be undertaken only at the expense of the author. All illustrations must be referred to in the text by Arabic Numerals (thus—Figure 3) the corresponding Arabic Numeral being clearly marked on the back of the illustration, together with the name of the author and the title of the article. Legends for illustrations must be typewritten in double space on a separate sheet of paper and clearly marked with the numerals corresponding to the appropriate illustrations.

Proofs

Galley proofs and engraver's proofs will be sent to the author and to the Editor for correction. A limited time will be allowed for return of proof from the Author, but in the event that Authors do not return proofs within the time allowed, the Editor may proceed to publish the article without awaiting return of proof from the Author.

Reprints

Authors' price list and order blank for reprints will be sent with galley proofs. Order for reprints must be returned with galley proofs to the Editor; otherwise reprints cannot be furnished at these prices.

CONTENTS

VOL. 3, No. 1 JANUARY, 1956